Programmatic and Individual-level Factors Associated with CD4 Cell Count at HAART Initiation and Survival Among Treatment-naïve Patients Initiating HAART in sub-Saharan Africa.

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Submitted in partial fulfillment of the
requirements for the degree of
Doctor of Philosophy
under the Executive Committee
of the Graduate School of Arts and Sciences

Columbia University

2014

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Abstract

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People living with HIV in low- and middle-income countries, on average, initiate antiretroviral therapy (ART) in the advanced stages of the infection (i.e. when the CD4 cell count has dropped below the recommended threshold for ART initiation) despite more than a decade since the start of scale-up of ART [1-4]. Late ART initiation is associated with higher patient morbidity and mortality, increased risk of secondary transmission in the population and higher healthcare cost [5-10]. Knowledge of HIV status is a critical first step to initiate ART [11-14]. Yet, half of the people living with HIV in sub-Saharan Africa are not aware of their status [15]. The World Health Organization, the Joint United Nations Programme on HIV/AIDS and other institutions support adoption of active screening for HIV (i.e. testing asymptomatic people for HIV) to help identify and treat people living with HIV before progressing to the advanced stages of the infection [11, 14, 16, 17]. The role of active screening on earlier initiation of ART and patient survival has not been examined. In this dissertation, I reviewed and synthesized the literature to identify barriers to ART initiation operating in low- and middle-income countries. I examined the role of active screening on patient CD4 cell count at ART initiation (a measure of HIV-disease progression) and survival, and investigated patient CD4 cell count at ART initiation as a potential mediator of the active screening-patient survival association. The databases Ovid Medline, PsycINFO, CINAHL, Scopus and Cochrane Reviews were searched as part of the literature review. Of 265 articles reviewed, thirty-five met the eligibility criteria and were therefore selected for the review. Mixed linear regression models with random intercepts and

Marginal Cox Proportional models with robust sandwich estimators of variance were fitted as part of the statistical analyses for this dissertation. Patient, programmatic, and contextual variables were considered for statistical adjustment. Data for the analyses came from twenty-nine HIV/AIDS care and treatment sites in Kenya, Uganda, and Tanzania participating in the International Epidemiologic Databases to Evaluate AIDS (IeDEA) initiative. Patient level data were collected from 45,359 subjects who initiated ART between 2003 and 2008 in the twenty-nine sites. Site programmatic and contextual level data were collected via two structured questionnaires. The critical review of the literature led to the identification of 1) individual, programmatic and societal-level barriers to HIV testing, enrolling into care, and ART initiation; and 2) barriers pertaining to lack of knowledge of HIV/AIDS and ART (e.g. HIV/AIDS symptomatology, ART benefits, ART toxicity), limited accessibility to services, poor quality of services, shortage of staff, and HIV-related stigma as the most prominent barriers. Results of the analyses show that patients in sites with predominantly "Active Screening Entry Points" initiated ART, on average, with CD4 cell counts 24 cells/μL higher than patients in sites with mainly "non-Active Screening Entry Points." However, the gain in CD4 cell count did not translate into a statistically significant estimate of survival advantage for these patients [HR (95% CI): 0.82 (0.64 – 1.06)] though the results are in the expected directions. The modest gain in mean CD4 cell count, and the documented benefits of active screening (e.g. high acceptability, increased number of patients tested and higher rate of identification of previously undiagnosed people living with HIV) support adoption of this intervention particularly in regions with a high HIV burden and where a low proportion of the population is unaware of their HIV status.

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Acknowledgements

As the African proverb ("it takes a village…") goes many have played a fundamental role in helping me reach this point. I'm thankful to my family (the Brito, Espinal, and Toro family) for nurturing me, loving me unconditionally and supporting my dreams. I am thankful to all my friends in and outside the U.S., especially those from Atlanta, who have shown me the true meaning of friendship. I am grateful to Rachel Albalak for believing in me, and professional and academic guidance. I am thankful to my wife Jessica Banaay for her patience as I completed this dissertation. To Allan Rosenfield whose generosity and vision made it possible for me to attend such a prestigious university, thank you. I am grateful to Ezra Susser for recruiting me and his determination to organize all the resources and support necessary to allow me to succeed. To Alan Berkman for his guidance, conviction and courage, thank you. To Liliane Zaretsky, the Department of Epidemiology, and ICAP for making me feel at home and supporting me during one of the most difficult periods in my life I am forever thankful. I am also grateful to my doctoral cohort, Russell McBride, Mary Kilty, Dana March, and my partner in crime Sarah Braunstein (Dr. B) for all their support, laughter and many long hours of studying. I am thankful to Denis Nash for always thinking outside the box, patience, humbleness and genuine concern for the well-being of others. To my committee, Denis Nash, Sharon Schwartz, Constantin Yiannoutsos, Luisa Borrell, Crystal Fuller, for their willingness to take on yet another doctoral student and in the process making me a better epidemiologist, muchisimas gracias. I am thankful to Gina Lovasi and Matt Lamb for sharing their seemingly endless knowledge of epidemiology whenever needed. Last but not least, to the people of my beloved birthplace the Dominican Republic, who like our brothers in other so-called Third-World countries struggle each day for their God-given right to live, thank you for being my inspiration to embark on this journey. It will be a privilege to serve you. Thank you all and others not mentioned for being my village!

Dedication

This work is dedicated to my loving family: mis bisabuelos (great-grandparents) - Inocencio "Papa-Prieto" Brito and Rosaura "Mamá Chala" Rivera-, mis abuelos biológicos y adoptivo (biologic and adoptive grandparents) - Sebastián Brito Rivera, Serafina Espinal Santana and Bélgica Pérez Gallurdo-, mis tíos y tías (aunts and uncles) - Yuli, José Miguel, Ricardo ("Kico"), Víctor, José Alfredo, Nelson, María Victoria, Cecilia, Juana, Odalis, Rosa, Marisela and Denis-, and mi mamá y padrasto (mother and step-father) - Violeta and Lupe - all who collectively raised me; mis hermanos (siblings) -Abimael, Tubal, and Eric - and primo-hermanos (closest cousins) - Katy, Victor, and David - whom I was fortunate to grow up with; mis tio abuelos y tia abuelas (great aunts and uncles) – Salomón, Crescencio ("Negro"), Ricardo, Félix, Ana, Dolores, and Catalina, - who help maintain a solid foundation for the family; mis sobrinos (Trevor, Tubal Jr, Angelina, Noah, Sebastián, Sofía, and Gabriela) whose love is the most pure; all of mis primos y primas (cousins) who are too many to mention but whose achievements as human beings and professionally inspire me and our younger generation; and to futuras generaciones (future generations) who will be the beneficiary of the love we have been blessed with. Nuestro amor es eterno e incondicional. Han sido y continuaran siendo la fundación que ayudan a desarrollarme como persona. I am blessed.

Chapter 1. Introduction

Introduction

Background

Three and a half decades after its emergence, the HIV epidemic remains a pressing public health challenges worldwide [18-20]. Globally, 35.3 million people are living HIV [15] and as many people have died since 1981 [21]. The impact of the epidemic has been disproportional with low- and middle-income countries accounting for most of the deaths and infections [15, 22, 23]. In sub-Saharan Africa, the region most heavily affected [15, 23, 24], the epidemic has caused social and economic upheaval forcing numerous countries to declare AIDS a national health emergency [24]. In this region, AIDS has reversed gains in life expectancy [25, 26] and development [27], significantly decreased agricultural productivity [25, 28], and increased under-5 mortality [29] and widow and orphan-headed households [30].

After the advent of antiretroviral therapy (ART) in 1996, HIV infection changed from a death sentence to a chronic treatable condition [31, 32]. Efforts led by the United States' President's Emergency Plan for AIDS Relief (PEPFAR), the Global Fund for AIDS, TB and Malaria and other international organizations [18], and strong political-will from low- and middle-income countries [15, 18, 27] have made ART available worldwide. Today 9.7 million people in low- and middle-income countries are currently on ART when only 300,000 were on treatment in 2002 [33]. Furthermore, over the years the distribution of ART has become more proportional to the HIV burden as 78% of those on treatment reside in sub-Saharan Africa [34]. The impact of these efforts is tangible. Approximately 5.5 million deaths have been averted in low- and middle-income countries since 1996, and HIV transmission has been reduced by 50% in some regions of these countries [15, 35]. In addition, labor productivity has increased, HIV-associated healthcare cost reduced, and the need for orphan care minimized [31, 36, 37].

The state of the epidemic today was aptly described in 2005 by Alan Berkman as "the best of times and the worse of times" [27]. Despite the progress, nearly 2 million adults in low- and middle-income countries acquire the virus each year [15]. Per the 2013 World Health Organization treatment guidelines, sixty-six percent of people who should be on ART in these countries are not receiving it, and millions are still dying each year [15]. Moreover, the full potential benefits of ART to individuals and the population as a whole have yet to materialize [38, 39] as most people living with HIV in these countries start treatment late (i.e. during the advanced, symptomatic stages of HIV disease when the CD4 cell count has dropped below the recommended threshold for ART initiation) [4].

Study Justification

Late ART Initiation

CD4 cell count is an important immunologic marker of progression of HIV infection and a key predictor of mortality [40-42]. The current World Health Organization treatment guidelines recommend initiation of ART before the CD4 cell count reaches less than 500 cells/μL [43]. Although it increased by as much as 83% relative to 2002, the median CD4 cell count at ART initiation for low-income countries was only 145 cells/μL by 2009 [4]. Middle-income countries registered a similar trajectory during this period with an increase from 87 to 155 cells/μL under the best case scenario [4]. Thus, even though ART has been available for a decade, patients in low- and middle-income countries generally start treatment at or below the 2003 World Health Organization threshold of 200 cells/μL [44].

The consequences of late ART initiation affect not only the individual but also the societies and economies of these countries. Late ART initiation is associated with higher patient morbidity and mortality, increased risk of secondary transmission in the population and higher healthcare cost [5-10]. The mechanisms leading to late ART initiation are complex. In the context of resource-limited settings, treatment availability has not translated into accessibility. As a decade of experience with ART delivery has shown, addressing late initiation of ART requires more than decreasing the cost of medication for low- and middle-income countries. It necessitates analyzing the context in which delivery occurs so that barriers and facilitators are identified.

Causes of Late ART Initiation

The causes of late ART initiation include both proximal and distal factors some of which are outside the control of individuals, and others which operate at different stage of the HIV treatment cascade (i.e. HIV diagnosis, enrollment in care, and ART initiation). HIV testing, and care and treatment programs are operating in the context of underfunded, poorly integrated healthcare systems [45-47]. Furthermore, these programs aim to deliver health services to a population with high rates of poverty and who reside in settings with weak overall infrastructure (e.g. transportation, housing) [46-48]. Consequently, preventive and consistent care, which can aid in the timely identification of people living with HIV, is not the norm [46]. Knowledge of HIV status is a critical first step to engage those living with HIV in the treatment cascade [11-14]. Yet, half of the people living with HIV in sub-Saharan Africa are not aware of their status [15] and would need to overcome personal and contextual barriers to receive a timely diagnosis. In response to these issues, the Joint United Nations Programme on HIV/AIDS and other

institutions have promoted adoption of active screening to compliment Voluntary Counseling and Testing [11, 14, 16, 17].

Active Screening of HIV

Active screening involves the routine offering of HIV testing and counseling to all individuals attending healthcare sites as part of standard care [11, 14, 17]. Unlike Voluntary Counseling and Testing, active screening is integrated within the healthcare system, and places the responsibility of initiating testing on the provider as opposed to the client who may be encumbered by lack of knowledge of HIV or perception of low risk [11, 17]. The existing literature shows that active screening increases the number of patients tested per provider and the rate of identification of HIV-positive individuals [11, 13, 49-51]. However, other studies show that a low proportion of those who test positive enroll into HIV care and treatment shortly after diagnosis. It is unknown whether active screening helps reduce late ART initiation and as a result improves patient survival in the context of resource-limited settings.

Methods and Objectives

Aims and Hypotheses

This dissertation centers on 1) assessing the role of active screening, a widely adopted intervention in low- and middle-income countries [33], on patient CD4 cell count at ART initiation and survival, and 2) testing patient CD4 cell count at ART initiation as a mediator of the active screening-patient survival relationship. It also reviews and synthesizes the literature to identify barriers to ART initiation. The dissertation has the following aims and hypotheses:

AIM I: To critically review and synthesize the literature examining barriers to timely initiation of ART in low- and middle-income countries.

AIM II. To determine the extent to which active screening is associated with 1) patient CD4 count at ART initiation and 2) patient survival among treatment naïve patients.

Hypothesis 1: HIV/AIDS care and treatment sites that conduct active screening will have 1) higher patient CD4 count at ART initiation compared with sites that do not conduct active screening.

Hypothesis 2: HIV/AIDS care and treatment sites whose primary entry points are associated with active screening (e.g. antenatal care units with Prevention of Mother to Child Transmission Programs) will have 1) higher patient CD4 count at ART initiation and 2) higher patient survival rates compared with sites whose primary entry points are not associated with active screening (e.g., Tuberculosis programs).

Hypothesis 3: The association between a site's primary entry points and patient survival will be mediated, at least in part, by patient CD4 count at ART initiation.

Methodological Approach

Chapter 2 addresses aim I (critical review of the literature). I searched the databases Ovid Medline, PsycINFO, CINAHL, Scopus and Cochrane Reviews to identify individual-, programmatic-, and societal-level barriers to HIV testing, enrollment into pre-ART care, and ART initiation. Eligible articles for this review met the following criteria: 1) describe barriers to HIV testing, enrollment into pre-ART care or ART initiation, 2) include adult men and non-pregnant women in the general population as opposed to solely specific subgroups (e.g.

intravenous drug users, commercial sex workers which were not included in this analysis), 3) focus on low- and middle-income countries, 4) present findings from qualitative or quantitative studies or systematic reviews, and 5) are peer-reviewed. Information on the year of publication, country/region study was conducted, study population, sample size, and study design was extracted. A list of all of the identified barriers was created, and the barriers were organized by treatment cascade stage (i.e. HIV testing, enrollment into pre-ART care, ART initiation), level of organization (i.e. individual-, programmatic-, societal-level), and theme (Knowledge/Information, Accessibility, Quality of Care, Stigma/Discrimination, Cultural/Gender Norms, Resources, Integration, and Policies). Lastly, the number of times a barrier was identified was tallied to determine those more commonly reported.

Aim II (relationship between HIV active screening, patient CD4 cell count at ART initiation, patient survival) is addressed in Chapters 3 and 4. In Chapter 3, separate analyses were performed to tests the association between the exposure variables "Active Screening" and "Active Screening Entry Points" and the outcome patient CD4 cell count at ART initiation. HIV/AIDS care and treatment sites were classified by "Active Screening" status for the first analysis, and by "Active Screening Entry Points" status for the second analysis. Mixed linear regression models with random intercepts were fitted for each analysis. Patient-, programmatic-, and contextual-level variables were considered for statistical adjustment.

In Chapter 4 I tested the association between "Active Screening Entry Point" and patient survival. In addition, patient CD4 cell count at ART initiation was tested as a mediator of the "Active Screening Entry Points"- patient survival association. Marginal Cox Proportional models with robust sandwich estimators of variance were fitted in this analysis. Patient-,

programmatic-, and contextual-level variables were also considered for statistical adjustment of the survival models.

Patient and site level data were used for the analyses performed in Chapters 3 and 4. A total of 45,359 patients who initiated ART between 2003 and 2008 in twenty-nine HIV/AIDS care and treatment sites provided data on demographic, clinical, laboratory and treatment status. The sites are located in Kenya, Tanzania and Uganda and participate in the International Epidemiologic Databases to Evaluate AIDS (IeDEA) (http://www.iedea-ea.org). The IeDEA initiative is a worldwide research collaboration established in 2005 to identify optimal treatment and prevention strategies across diverse economic, geographical, and cultural settings. Programmatic and contextual data from participating sites were collected using two structured questionnaires: the East Africa Brief Follow-up Questionnaire and the IeDEA site assessment tool.

Chapter 2. Individual, Programmatic, and Societal barriers Associated with Late ART Initiation in Low- and Middle-Income Countries: A Comprehensive Review of the Literature Published During the Scale-up of ART.

Introduction

As we enter the fourth decade since its emergence, the HIV epidemic remains a major global public health challenge. Worldwide, an estimated 35.3 million people are living with HIV with ninety-five percent residing in low- and middle-income countries [15, 22, 23]. The advent of highly active antiretroviral therapy (ART) in 1996 dramatically changed the prognosis of the infection from a death sentence to a chronic treatable condition [31, 32]. The global effort to make ART available in low- and middle-income countries has had measurable success. Approximately 9.7 million people living with HIV are now on treatment in low- and middle-income countries, an estimated 5.5 million AIDS-related deaths have been averted since 1996, and new HIV-infections among adults have been reduced by 30% since 2001 in part due to ART's ability to reduce viral load [15, 33]. Furthermore, economic data show that the returns on investments of ART scale-up in low- and middle-income countries far exceeds its cost partly due to increased labor productivity, prevention of orphan care, and decrease of healthcare cost [31, 36, 37].

Many challenges to control the epidemic remain, however, especially in low- and middle-income countries. Approximately 36% of people in sub-Saharan Africa, the region most heavily affected by the epidemic, have never been tested for HIV and half of those living with HIV are not aware of their status [15, 52]. HIV/AIDS remains among the leading causes of disability and death in the region [19, 20]. Sixty-six percent (under 2013 WHO treatment guidelines) of the 28.6 million people eligible for ART in low- and middle-income countries are not receiving treatment and thus are at increased risk of premature morbidity and mortality and of transmitting the virus [15]. An estimated 1.9 million new infections occur annually among adults in these countries [15]; over 90% of the 1.6 million annual AIDS-deaths occur in low- and middle-

income countries [15, 35]. ART patients in low and middle-income countries are three-to-four times more likely to die during the first year of treatment than those in high-income countries [5]. Thus, the full clinical, societal and economic potential of ART is yet to be achieved. At the heart of these challenges is late ART initiation (starting ART during the advanced, symptomatic stages of HIV disease).

Since 2003, the World Health Organization has recommended that HIV positive adults and adolescents initiate ART *before* their CD4 cell count drops below 200 cells/μL to avoid the consequences of late ART initiation [41, 43, 44, 53]. The 2010 guidelines increased the threshold for ART initiation to 350 cells/μL and the 2013 guidelines to 500 cells/μL [43, 54]. Late ART initiation is associated with higher morbidity and mortality, increased risk of secondary transmission and higher healthcare costs [5-10]. Yet, people living with HIV in low- and middle-income countries, on average, initiate treatment below 200 cells/μL despite more than a decade since the start of ART scale-up efforts in these countries [1-4].

The barriers to late ART initiation include both proximal and distal factors. Some of these barriers exert their effect even before HIV is diagnosed. As shown by the conceptual diagram in Figure 1 [1], the HIV treatment cascade can be divided into three stages following HIV infection: HIV diagnosis, enrollment in care, and ART initiation. Delays at any stage along the cascade can lead to late ART initiation. Four different possible scenarios (Pathways A-D) presented in Figure 1 lead us to three key conclusions which can be applied in investigating barriers to late ART initiation:

1) An early diagnosis soon after infection occurs is necessary to avoid late ART initiation. As shown by Pathway A, patients diagnosed in the advanced stages of the infection have no other alternative but to initiate treatment late.

2) Although necessary, an early diagnosis is not sufficient to guarantee timely ART initiation. Patients must be referred to and promptly linked with HIV/AIDS care shortly after diagnosis for continual monitoring until he or she is eligible for ART initiation. As shown by Pathways B and C, delays in enrollment in pre-ART care and/or ART initiation will minimize the potential benefits of an early diagnosis.

3) As shown by Pathway D, it is crucial that barriers to each stage of the treatment cascade are addressed to prevent late ART initiation.

In summary, the scale-up of ART in low- and middle-income countries has led to considerable benefits for individuals and societies. However, late ART initiation, which is associated with premature morbidity and mortality, secondary HIV-transmission, and higher healthcare cost, remains a formidable challenge. Using Figure 1 as a guide, this review summarizes individual-, programmatic-, and societal-level factors identified as barriers to late ART initiation in low- and middle-income countries.

Methods

Search Strategy

Three separate searches were conducted using the same set of databases to identify barriers to 1) HIV testing, 2) enrollment into pre-ART care, and 3) ART initiation. The databases Ovid Medline, PsycINFO, Cochrane Reviews, CINAHL, and Scopus were searched (See "Search Strategy", Appendix A for other databases considered). We used the following search terms in different combinations to search the literature for barriers: "HIV", "AIDS/or Acquired Immunodeficiency Syndrome", "barriers", "developing countries/or resource limited", "low income countries", "middle income countries", and "Africa"; the following terms were used in conjunction with the aforementioned to subset the search to specific stages within the treatment cascade: "testing", "HIV testing", "care/or patient care", "HIV care", "AIDS care", "pre-ART", "antiretroviral drugs/or HAART", "HAART/Antiretroviral Therapy/Highly Active." The search was limited to articles published from 1996 (marking the advent of ART) to August 2012 and was limited to the English language. To supplement the search, we used the database search option "Find Similar" for the most relevant articles, reviewed the bibliography of review and other key articles, and added relevant articles from preliminary literature searches conducted in preparation for this manuscript (e.g. dissertation proposal).

Study Selection

Selection of articles began by screening the titles and/or abstracts of articles identified during the search. Those articles whose subject matter did not pertain to the focus of this review were excluded. The remaining articles were then assessed for eligibility. Eligible articles met the following criteria: 1) describe barriers to HIV testing, enrollment into pre-ART care or ART initiation, 2) include adult men and non-pregnant women in the general population as opposed to

solely specific subgroups (e.g. intravenous drug users, commercial sex workers which were not included in this analysis), 3) focus on low- and middle-income countries, 4) present findings from qualitative or quantitative studies or systematic reviews, and 5) are peer-reviewed.

Review

Eligible articles were reviewed to extract key study characteristics, and identify barriers. Information on the year of publication, country/region study was conducted, study population, sample size, and study design was extracted. The barriers reported in each article were compiled, and then organized by whether they impacted HIV testing, enrollment into pre-ART care, and/or ART initiation in accordance with Figure 1. Within these three stages, the barriers were subdivided by whether they arise from individual, programmatic or societal level. Furthermore, within these levels, barriers were organized into eight themes (Knowledge/Information, Accessibility, Quality of Care, Stigma/Discrimination, Cultural/Gender Norms, Resources, Integration, and Policies). The themes were based on the similarities or patterns observed among the barriers reported. For example, barriers pertaining to misconceptions of treatment, and unawareness of AIDS symptoms were grouped into the "Knowledge/Information" theme. Lastly, we tallied the number of times a barrier was identified to determine those more commonly reported.

Results

Study Selection and characteristics

A total of 265 articles were identified during the search with twelve of these identified via a review of bibliographies of other articles (see Figure 2, and Table 1 for a detailed list of the number of articles identified by search terms, selected for review and meeting the eligibility criteria). Eighty-two (30.9%) were kept after the initial screen. Of these, thirty-five (42.7%) met the eligibility criteria and were included in the final review.

Table 2 shows the key characteristics of the thirty-five articles. The years of publication range from 2001 to 2012. The study populations for thirty-three of the articles came from four regions: 1) sub-Saharan Africa (87.9%), 2) Asia (6.1%), 3) Middle East/Northern Africa (3.0%), and 4) the Caribbean (3.0%). Among the remaining two articles, one included twenty-nine countries from different parts of Africa (including Northern and sub-Saharan African) and the other an unspecified number of low- and middle-income countries in Latin America and Africa. South Africa was the focus for almost half (44.8%) of the twenty-nine articles from sub-Saharan Africa. The study populations included: adult men and women of varying HIV status, people living with HIV at different stages of the infection, community members, healthcare workers (e.g. counselors, physicians), NGO directors, health sites and healthcare systems. Most of the studies were quantitative (45.7%), followed by qualitative (31.4%), literature review (14.3%) and mixed qualitative/quantitative methods (8.6%).

Barriers to HIV Testing

Twenty-eight barriers to HIV Testing were identified (See Table 3). Some of the individual-level barriers varied depending on whether AIDS symptoms were apparent. Those without symptoms did not see themselves at risk and therefore did not see a need for testing [20,

55]. Among those with symptoms, lack of knowledge of HIV symptomatology, having a fatalistic attitude towards HIV/AIDS, or unwillingness to confront HIV/AIDS while on tuberculosis treatment inhibited those who may do so otherwise from getting tested [56-60]. Factors limiting an individual's accessibility to testing included the cost of testing, and having inflexible work schedule [20, 55, 61, 62]. Endorsing AIDS-related stigma, and fear of experiencing stigma and of the consequences of testing positive (e.g. necessary changes in behavior and priorities, discrimination) were also identified as barriers [55-59, 63-67]. Other barriers included concerns about quality of care (e.g. protection of confidentiality, lack of empathy for those who test positive) [56-59]; and lack of autonomy for women who want to make decisions about their health [56, 64].

At the programmatic-level, limited access to testing due to lack of testing services particularly in rural areas, financial cost, inconvenient hours of operations and long waiting time were identified as barriers to testing [20, 55, 57, 68]. Shortage of staff, and lack of training and support (e.g. emotional support to reduce stress, medical supplies) for the staff reportedly discouraged individuals willing to get tested [58, 68]. Inadequate counseling rooms led to concerns of confidentiality when discussing test results [58]; and lack of services addressing barriers particular to men (e.g. men's perception of risk taking as part of masculinity or healthcare is only for women or when one is symptomatic) was identified as limiting their participation [67].

HIV/AIDS morbidity and mortality have diminished the public health labor force and thus has become a societal barrier [69]. Traditional views of masculinity (e.g. proving one's manhood by not seeking medical care unless physical strength is weakened) were identified as societal barriers [20, 67]. Lastly, discrimination, violence and implementation of discriminatory

policies towards people living with HIV discouraged individuals from seeking HIV testing [57, 63, 65, 68, 70].

Barriers to Enrollment into Pre-ART Care

Table 4 lists the barriers to enrolling into pre-ART care. A total of twenty-six barriers were identified. At the individual-level, not being aware of one's HIV status, and again lack of knowledge of HIV/AIDS were identified as barriers this time to pre-ART care [7, 57, 62, 71, 72]. Concerns about the side-effects of ART and of those that could arise from alcohol consumption while on treatment also hindered enrolling into care [7, 9, 72]. Factors associated with age (e.g. knowledge of HIV/AIDS), sex (gender norms), low socioeconomic status (poverty), having inflexible work hours, distance to the health site, financial cost, and unfamiliarity with navigating the health system affected accessibility to care [7, 61, 62, 67, 71, 72]. Fear of stigma, and not being able to disclose one's HIV status prevented people living with HIV from enrolling into care [7, 57, 59, 65, 72]. Lastly, concerns about the quality of care were again identified [71-73].

Programmatic-level barriers included the site's limited hours of operation particularly for those employed [72]. Poor quality care at health sites (e.g. lack of confidentiality), and staff's negative attitudes towards patients and co-workers suspected of being HIV positive discouraged people living with HIV (including health practitioners) from seeking care [58, 74]. At the societal, the limited pool of staff available for recruitment, as a consequence of HIV/AIDS, hindered the provision of quality care [69] . Traditional gender norms for both men and women were identified as social barriers as well as observed violence, stigma, and government policies limiting the rights of people living with HIV [63, 65, 67, 68, 70, 74].

Barriers to ART Initiation

Fifty-two barriers to ART initiation were identified and are listed in more details in Table 5. These include those identified earlier as barriers to testing and enrolling into care (lack of symptoms, knowledge, fear of side effects and waiting until TB treatment was complete before initiating ART) [9, 52, 57, 60, 65, 69, 74-77]. HIV-related morbidity as the infection progresses, financial strain (due to unemployment, lower socioeconomic status), level of affordability of treatment (including fees, ART and laboratory tests), and logistics (e.g. cost and access to transportation, visit waiting time) limited accessibility to treatment [10, 60, 61, 65, 69, 72, 73, 76, 78-80]. Not receiving quality pre-ART care (lack of or inconsistent CD4 monitoring, sub-standard treatment from clinical staff), and changing health site after being diagnosed were also identified as barriers [9, 60, 65, 72-74, 81, 82]. Barriers related to cultural/gender norms such as the expectation of women to care for sick relatives were also reported [61, 67, 76, 77]. Lastly, HIV-related stigma and factors associated with stigma (e.g. lack of social support, inability to disclose, age and sex differences in disclosure) were again identified as barriers [9, 10, 57, 60, 65, 72, 74-77, 80, 81].

Programmatic-level barriers to ART initiation include high patient-provider ratio and high rate of staff turnover, the staff's limited knowledge of ART and inability to train them, and shortages in medication and equipment [52, 60, 67, 69, 74, 83-85]. The staff's disregard for protecting patient confidential information and poorly maintained health sites impacted quality of care and discouraged patients from seeking treatment [61, 69, 79]. Factors related to the management of patients and the staff were also identified. These included: 1) weak referral systems to bring diagnosed patients into care in a timely fashion, 2) sub-optimal system to prevent patients from being lost to follow-up especially for those considered not yet eligible for

care, 3) overly restrictive or inflexible requirements for ART preparedness (e.g. requiring "treatment buddies" and participation in adherence training before starting ART) even at the expense of losing patients too poor to cover the transportation cost of a "buddy" or too sick to complete adherence training before starting ART, 4) inconsistent application of the sites treatment guidelines for ART initiation, and 5) lack of task shifting policy to alleviate shortage of physicians [60, 74, 77, 83-85]. Barriers related with communication included the staff not speaking in the local native language of patients, and insufficient communication between counselors and physicians [52]. Stigma from staff towards patients and fellow staff discourages ART initiation for both patients and staff [52, 62, 70, 76, 77, 79]. The lack of collaboration between ART programs and tuberculosis treatment services or traditional healers were among the barriers associated with poor integration of services which as a consequence limited referral of HIV patients into care [52, 69, 71]. Lastly, persistent adoption of outdated national treatment guidelines (e.g. 2002 WHO ART guidelines which recommends treatment only for patients at CD4 cell counts below 200 cells/μL) was noted as a barrier to ART for patients eligible under current WHO ART guidelines [10, 83]; the absence of guidelines for the private sector also led to late treatment initiation [68].

At the societal level, HIV-related morbidity and mortality has contributed to shortages of staff reducing the ability to address high patient-provider ratio and staff turnover rates [69]. Lack of knowledge of ART or propagation of inaccurate information about ART in the general population hinders initiation of treatment as it adds to preexisting levels of HIV-related fears [74]. Factors identified as barriers to HIV testing and enrollment into care (e.g. cultural and gender norms, and stigma) were also reported as societal barriers to ART [61, 63, 65, 67, 68, 70, 74-76, 79]. Finally, the lack of effective government policies to address social inequalities

limiting access to ART (e.g. unemployment, disparities in health) or enforcement of policies which inadvertently lead to unequal access to treatment (e.g. requirement of government-issued identification to receive ART) were reported as barriers [52, 61, 69, 70, 78, 79].

Prevalent Barriers

The most commonly reported barriers to HIV testing pertained to the Stigma/Discrimination, 35% (10/28), and Accessibility, 18% (5/28) themes. These themes were also the most commonly reported for enrollment into pre-ART care, 27% (7/26) and 23% (6/26), respectively. Barriers pertaining to the Quality of Care, 31% (16/52), and Stigma/Discrimination, 19% (10/52), themes were the most commonly reported for ART initiation.

Discussion

Our literature review of thirty-five articles on the barriers to ART initiation in low- and middle-income countries show that the barriers to treatment 1) impact all of the stages on the treatment cascade (HIV diagnosis, enrollment into care, ART initiation), and 2) within each stage, operate at the individual, programmatic and societal-level. As hypothesized by the conceptual model (Figure 1), distal as well as proximal barriers to ART initiation were identified. Therefore, interventions which do not address barriers to HIV diagnosis and enrollment into pre-ART care may fail to materially alleviate late ART initiation. Furthermore, interventions for late ART initiation should be multifaceted so that in addition to individual level factors (e.g. being aware of one's HIV status, financial cost of care), programmatic deficiencies (e.g. poor quality of care, weak referral mechanisms) and societal barriers (e.g. stigma/discrimination towards people living with HIV, lack of knowledge of HIV in the community) are addressed concurrently.

We found that barriers associated with 1) lack of knowledge of HIV/AIDS and ART (e.g. HIV/AIDS symptomatology, ART benefits, ART toxicity), 2) limited accessibility to services, 3) poor quality of services, 4) shortage of staff, and 5) prevalent HIV-related stigma were identified across all three stages of the treatment cascade. Barriers associated with accessibility to services and stigma/discrimination were reported most often. We argue that barriers associated with lack of knowledge of HIV/AIDS and ART, limited accessibility to services, poor quality of services, and shortage of staff (1-4 above) are a consequence of the weak or non-existing healthcare system into which ART has been introduced.

With few exceptions (e.g. Cuba's healthcare system), healthcare systems in low- and middle-income countries are in a weak state and are poorly integrated due to underinvestment, decades of neglect by the government and implementation of structural adjustment programs [45-47]. Throughout the 1980s and 1990s, the International Monetary Fund's and the World Bank' promoted economic policies, known as structural adjustment programs, intended to achieve long-term economic growth in less developed countries [86, 87]. One of the components of these policies was for the national government to substantially reduce spending on health and welfare programs [27, 87, 88]. The consequences of these policies on an already underfunded systems serving predominantly impoverished populations were dire [87, 88]. These included reductions in demand for health services (as household incomes decreased as a result of structural adjustment programs), decreases in access to health services, restrictions in hiring of staff even as the population increased or diseases spread, and cuts in maintenance of health sites and equipment [46, 86, 88]. It is no coincidence that these consequences are the same structural barriers identified in the literature.

Though it would be impractical to recommend restructuring entire healthcare systems to address barriers to ART initiation, a sound understanding of the context in which HIV care and treatment was introduced is crucial to develop more comprehensive, multifaceted, effective public health approaches to address these barriers. Conditions such as HIV/AIDS require life-long monitoring of people with the infection and continuous testing of those at risk for the infection. Unless the structural barriers which prevent large segments of the population in less developed countries from engaging consistently with the healthcare system are addressed, the effectiveness of interventions to combat late ART initiation will be limited.

HIV-related stigma was among the most commonly identified barriers in the literature. Stigma in the context of HIV has a long history. It was brought to the forefront by public health leaders (e.g. Jonathan Mann) as early as the mid-1980s [89]. Blame, and exaggerated fears of infectiousness and death have been associated with HIV/AIDS since emergence of the epidemic [57]. Further association of HIV with socially marginalized groups (e.g. gays, intravenous drug users, commercial sex workers) and culturally-sensitive topics such as sex and drug-use has amplified HIV-related stigma, and as shown by our findings create a powerful barrier at every stage of the treatment cascade and every level of organization [68, 70]. The notion that HIV-related stigma would diminish as treatment becomes widely available is not supported by the frequency with which stigma was reported as a barrier even in the era of ART [65].

Certain limitations should be noted. Given the nature of qualitative studies, we cannot determine the extent to which the identified factors hinder progression through the stages of the treatment cascade. Though results from quantitative studies can help shed light on this matter, those identified were cross-sectional in nature and thus should be interpreted with caution. We could not quantify the significance or prevalence of the barriers (e.g. attributable fraction associated with late ART) beyond the frequency with which they were reported. To avoid limiting generalizability, we excluded studies focusing exclusively on important subgroups (e.g. migrant workers, commercial sex workers, intravenous drug users) who may face unique barriers to accessing care. Since neither of these important issues was the focus of our study, future studies should focus on 1) determining which of the identified barriers play a bigger role in limiting access to care, and 2) in assessing differences and similarities between these barriers and those faced by specific subgroups. The results were summarized for all low- and middle-income countries which vary in terms of HIV prevalence, economic power, state of healthcare system,

and cultural practices. Nonetheless, our findings are applicable to countries and/or regions affected by limited access to care, poverty, weak healthcare infrastructure and stigma. Lastly, as is common with most literature reviews we cannot rule out publication bias.

Our study has several strengths. The articles identified covered four different regions which carry the biggest burden of the HIV epidemic. Studies from sub-Saharan Africa, the region with the highest HIV-prevalence, and South Africa, the country with the largest number of people living with HIV, were well-represented. The years of publication of the articles (2001 to 2012) coincide with the period of major scale-up of ART in low- and middle-income countries. The studies included both quantitative and qualitative methods using a mixture of study designs (e.g. focus groups, in-depth interviews, surveys). Finally, our focus and results were comprehensive as we succeeded in identifying barriers operating at the individual, programmatic, and societal level and at multiple stages of the treatment cascade.

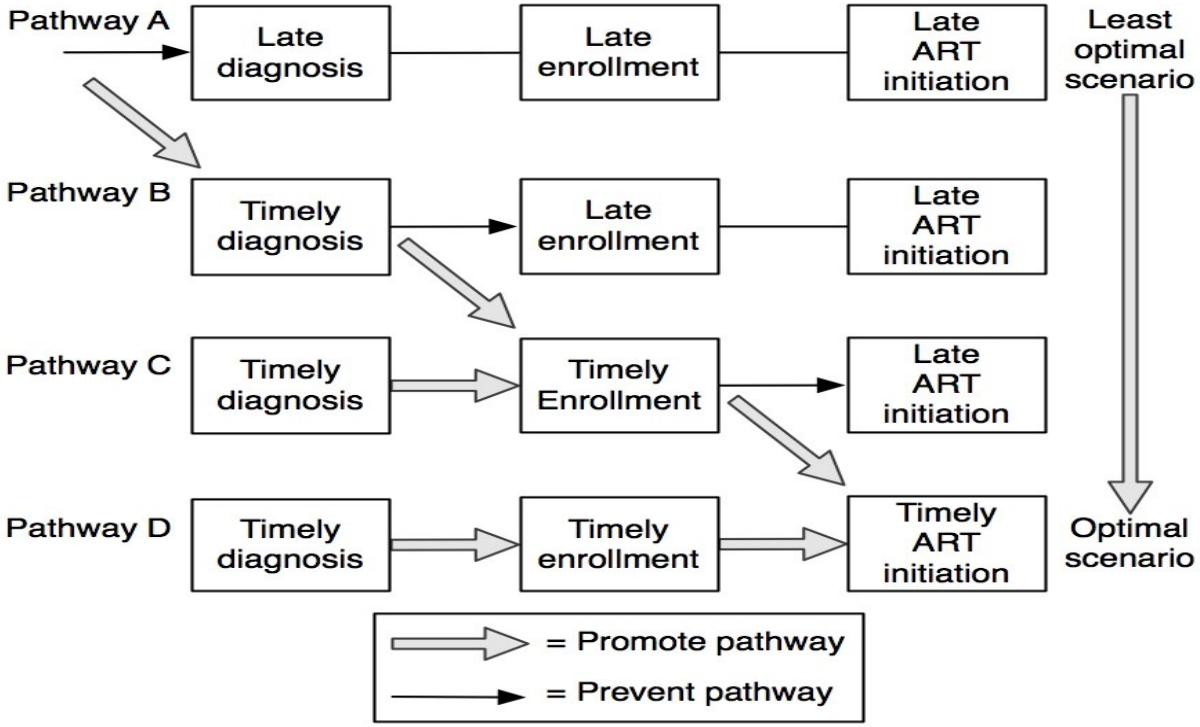
Conclusions

The scale-up of ART in low- and middle-income countries has been ongoing for over a decade and these efforts have helped reduce the consequences of the HIV-epidemic. Yet millions of people eligible for ART in these countries are not receiving treatment, and the risk of death even for those on ART is considerably higher than for patients in developed countries [5, 15]. Late ART initiation limits the potential of ART to diminish HIV-related morbidity and mortality, the incidence of new infections and economic loss [5-10]. The barriers contributing to late ART initiation impact all stages of the treatment cascade (HIV diagnosis, enrollment into pre-ART, ART initiation), operate at the individual, programmatic, and societal-level and include: 1) lack of knowledge of HIV/AIDS and ART (e.g. HIV/AIDS symptomatology, ART benefits, ART toxicity), 2) limited accessibility to services, 3) poor quality of services, 4) shortage of staff, and 5) prevalent HIV-related stigma. Unless comprehensive, multifaceted interventions to late ART initiation are implemented or the healthcare system is strengthened, the availability of ART in the context of developing countries will not necessarily translate into accessibility for all who need it.

Tables and Figures

Barriers to ART Initiation

Figure 1. The Effects and Consequences of Barriers at Each Stage of the Treatment Cascade on Initiation of Antiretroviral Therapy for People Living with HIV in Low- and Middle-Income Countries.



Source: Lahuerta M, et al. The Problem of Late ART Initiation in Sub-Saharan Africa: A Transient Aspect of Scale-up or a Long-Term Phenomenon? *Journal of Health Care for the Poor and Underserved* 2013, 24:359-383.

Figure 2. Flow Chart of Studies Identified, Selected for Review and Included for Review of Literature on Barriers to Initiation of Antiretroviral Therapy in Low- and Middle-income Countries.

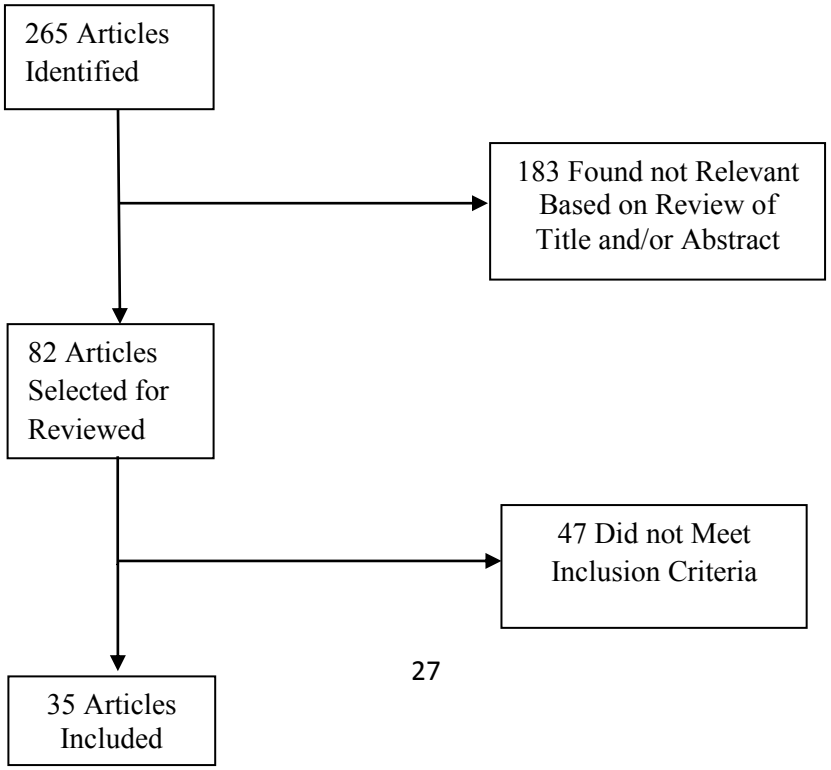


Table 1. Number of Articles Identified/Screened, Reviewed and Selected for Literature Review, by Stage of Treatment Cascade.

Topic	Search Term Combinations	Source	No. of Articles Identified/Screened	No. of Articles Reviewed	No. of Articles Eligible
Barriers associated with HIV	"HIV+Barriers+Africa"; "HIV+Barriers+ Developing Countries/or Resource limited"	Ovid Medline	13	7	3
Barriers to HIV testing	"HIV+Barriers+Africa"; "HIV+Barriers+ Developing Countries/ or Resource Limited"; "Barriers+Africa+HIV Testing"; "Barriers+Developing Countries/or Resource-limited+HIV testing";	Ovid Medline	59	8	5
Barriers to HIV and AIDS care	"HIV+Barriers+Africa+ AIDS or Acquired Immunodeficiency Syndrome +Care/or Patient Care"; "HIV+Barriers+Developing Countries/Resource-limited+ AIDS or Acquired Immunodeficiency Syndrome+ Care/or Patient Care"; "Barriers+ Africa+HIV Care"; "Barriers+ Developing Countries/ Resource-limited+HIV Care"; Barriers+ Developing Countries/ Resource-limited+AIDS Care;	Ovid Medline	31	8	2

Table 1 (Cont'd). Number of Articles Identified/Screened, Reviewed and Selected for Literature Review, by Stage of Treatment Cascade.

Topic	Search Term	Source	No. of Articles Identified/Screened	No. of Articles Reviewed	No. of Articles Eligible
Barriers to HIV testing	"HIV Testing+Barriers+ Africa"; "HIV Testing+ Barriers+Developing Countries";	PsycINFO	24	6	5
Barriers to ART	"Barriers+Africa+Antiviral Drugs/or HAART; "Barriers+Developing Countries+Antiviral Drugs or HAART"	PsycINFO	24	9	3
Barriers to ART*	"Barriers+Developing Countries+HAART/ Antiretroviral Therapy/ Highly Active"; "Barriers+ Africa+HAART/ Antiretroviral Therapy/ Highly Active";	Ovid Medline	45	15	5
Barriers to HIV testing	"HIV+Testing+ Barriers+Africa"	Cochrane	20	1	0

Note: *Employed search strategy "Find Similar" for key, relevant articles identified.

Table 1 (Cont'd). Number of Articles Identified/Screened, Reviewed and Selected for Literature Review, by Stage of Treatment Cascade.

Topic	Search Term	Source	No. of Articles Identified/Screened	No. of Articles Reviewed	No. of Articles Eligible
Barriers to HIV testing	"HIV+Testing+Barriers+ Africa"; "HIV Testing+ Barriers+Africa"	CINAHL	4	1	0
Barriers to HIV Care	"HIV+Care+Middle income countries"; "HIV+pre-ART+ Low income countries";	Scopus	12	2	0
Barriers to HIV Testing, pre-ART Care, and/or ART	Not Applicable	Bibliography of articles reviewed	12	9	4
Barriers to HIV Testing, pre-ART Care, and/or ART	Not Applicable	Dissertation proposal	21	16	8
		Total	265	82	35

Table 2. Key Characteristics of the Thirty-five Articles Selected for the Literature Review.

References	Publication Year	Country/ Region	Population	Sample Size	Study Design
Benotsch[63]	2008	29 Countries from Different Regions in Africa	Directors of NGOs	29 HIV-Prevention NGOs	Cross-Sectional
Boyer[78]	2009	Yaoundé, Cameroon	ART and ART eligible patients in six public hospitals	N=707; 33% male; mean age: 35 years	Cross-Sectional
Cleary[79]	2012	Four provinces representing two urban and two rural areas, South Africa	ART patients aged ≥ 18 from 12 health sites in four provinces	N=1,267; 26.5% male; mean age: 37.3 years	Cross-Sectional
Daftary[56]	2007	Durban, South Africa	HIV tested Tuberculosis patients (47.6% HIV+, 23.8% unknown status)	N=21; 47.6% males; mean age: 31.9 years	Phenomenological
Dong[52]	2007	KwaZulu-Natal, South Africa	Healthcare staff, traditional healers, patients, community members accessing care or residing near hospital and referral site	Unspecified	Case Study
Fitzgerald[75]	2009	KwaZulu-Natal,	HIV+ men enrolled in HIV treatment programs, their family members and staff	8 HIV+ men; 9 family members who provide support for the men; information on age not provided;	Phenomenological and Case Study

Table 2 (Cont'd). Key Characteristics of Thirty-five Articles Selected for the Literature Review.

References	Publication Year	Country/ Region	Population	Sample Size	Study Design
Fox[73]	2010	Livingstone, Choma District, Lusaka, Zambia	Confirmed and suspected HIV+ individuals believed to be eligible for ART	N=800 (400 on ART, 400 not on ART); 33% male; information on age not reported.	Cross-Sectional
Fredlund[83]	2007	KwaZulu-Natal, South Africa	Nine clinics and one hospital providing HIV care and treatment	N=10 health units providing ART to 1,311 patients 2 years after program initiation	Case Study
Govindasamy [72]	2011	Western Cape, South Africa	Individuals newly diagnosed with HIV through a mobile unit	N=192; 59.5% males; mean age: 34.8 years.	Cross-Sectional
Hatcher[7]	2012	Nyanza Province, Kenya	HIV+ adults aged ≥ 18 years not previously enrolled in HIV care	N=483; 26.3% male; information on age not reported	Cross-Sectional
Kielmann[68]	2005	Pune, India	Private health practitioners	N=27; 78% with ≥ 10 years of experience	Phenomenological
Kumarasamy [61]	2007	India	Men and women in need of HIV testing, care and treatment	Not applicable	Literature Review
Kumwenda [84]	2011	Blantyre, Malawai	HIV+ postpartum ART eligible women	N=803; mean age: 27.8 years	Cross-Sectional

Table 2 (Cont'd). Key Characteristics of Thirty-five Articles Selected for the Literature Review.

Publication References	Country/ Year	Region	Population	Sample Size	Study Design
Loubiere[60]	2009	Various provinces, Cameroon	Adult HIV+ patients attending HIV services	N=2,566; 28.7% males; mean age: 36.7 years.	Cross-Sectional
Louis[71]	2007	Hinche, Haiti	HIV+ adults ≥ 18 years in pre-ART care at St. Therese Hospital	N=31; 51.6% males; mean age: 39.5 years.	Cross-Sectional and Phenomenological
Maman[64]	2001	Dar es Salaam, Tanzania	HIV+/- men and women, and HIV serodiscordant couples	N=15 women, 17 men and 15 couples	Phenomenological
Meiberg[57]	2008	Polokwane, South Africa	Black undergraduate (86%) and postgraduate university students	N=72; 48.6% males; ages 18-36 years.	Phenomenological
Morin[55]	2006	Epworth and Seke, Zimbabwe	Community members attending six open-air marketplaces	N=1,099; 58.3% males; mean age: 29.2 years.	Cross-Sectional and Phenomenological
Mqimeti[58]	2011	The Greater Tzaneen Sub-District, South Africa	Voluntary Counseling and Testing counselors working at hospitals and clinics	N=60; 10% male; 50% between ages of 40-49	Cross-Sectional
Msellati[80]	2003	Abidjan and Bouake, Côte d'Ivoire	Pre-ART and ART patients in eight health centers	N=711; 51.1% male; mean age: 35.1 years	Cross-Sectional

Table 2 (Cont'd). Key Characteristics of Thirty-five Articles Selected for the Literature Review.

Publication References	Country/ Year	Region	Population	Sample Size	Study Design
Mshana[65]	2006	Kisesa District, Tanzania	Recently diagnosed HIV patients; community members	N_1=12 HIV+ adults; 16 groups of 8-12 community members; Information on age and sex not provided	Phenomenological and Case Study
Muhamadi[74]	2010	Iganga District, Uganda	ART patients and community members living with or caring for ART patients	N_1=20 ART patients; 45% males; mean age: 36.4 years; N_2=112 community members; information on age or sex not provided.	Phenomenological and Case Study
Murray[76]	2009	Lusaka, Zambia	HIV+ breastfeeding mothers participating in a cohort study of mother-to-child transmission of HIV through breast milk and key informants (community members, cohort study staff, health practitioners)	N_1=41 breastfeeding mothers; N_2=33 key informants (18 community members, 3 churh/home-based care team members, 7 clinic staff members, 5 cohort study staff); information on sex and age not provided.	Phenomenological and Case Study
Nkuoh[20]	2010	Mbingo Village, Cameroon	Adult fathers with at least one child	N=252; 100% males; mean age: 49 years	Cross-Sectional
Ojikutu[69]	2007	South Africa	Not applicable	Not applicable	Literature Review

Table 2 (Cont'd). Key Characteristics of Thirty-five Articles Selected for the Literature Review.

Publication References	Country/ Year	Region	Population	Sample Size	Study Design
Opuni[81]	2009	Soweto and Johannesburg inner city, South Africa	HIV+ adults using clinical HIV services in the public and private sector; household members	N_1=510 HIV patients; 20% male; mean age: 35.7 years; N_2= 777 household adults; 45% male, mean age: 35.7 years.	Cross-Sectional
Parkes-Ratanshi[77]	2010	Masaka District, Uganda	ART eligible patients in pre-ART care; ART Patients	N_1=957 pre-ART patients; N_2=48 ART patients	Cross-Sectional and Phenomenological
Parrott[9]	2011	Karonga District, Malawi	ART patients enrolled in an HIV cohort study	N=60; 46.6% male; median age: 37 years	Cross-Sectional and Phenomenological
Pitpitan[66]	2012	Cape Town, South Africa	Individuals attending informal drinking establishments	N=2,572; 65.4% male; mean age: 32.6 years	Cross-Sectional
Remien[67]	2009	Middle East and North Africa	Men and women in need of HIV testing, care, and treatment	Not applicable	Literature Review
Sendagire[10]	2012	Kampala, Uganda	ART naïve and newly registered ART patients	N=326; 33% male; mean age: 34 years	Cross-Sectional
Skinner[70]	2004	South Africa	Not applicable	Not applicable	Literature Review

Table 2 (Cont'd). Key Characteristics of Thirty-five Articles Selected for the Literature Review.

Publication References	Country/ Year	Region	Population	Sample Size	Study Design
Souteyrand [62]	2008	Low- and Middle-income countries	Healthcare systems	Not applicable	Literature Review
Tayler-Smith[85]	2010	Thyolo District, Malawi	Pre-ART and ART patients	N=1,633; 34.1% males; Mean age: 34 years	Prospective Cohort
Van Dyk[59]	2003	All provinces, South Africa	Community members	N=1,422; 37.8% male; Median age: 32.3 years	Cross-Sectional

Table 3. Individual, Programmatic, and Societal Level Barriers to HIV Testing Reported in Low- and Middle-income Countries, 2001-2012.

Level of Organization	Theme	Barrier
Individual	**Knowledge/ Information:**	1. Perceived low HIV risk/lack of symptoms; 2. Lack of knowledge on HIV and benefits of treatment; having a fatalistic attitude; 3. Unwillingness to deal with both TB and HIV simultaneously;
	Accessibility:	1. Not knowing where to test; 2. Financial cost, time requirements; 3. Inflexible work hours/occupation;
	Quality of Care	1. Concerns about the quality of care at health site (e.g. protection of confidentiality, training of staff, lack of empathy);
	Stigma/ Discrimination:	1. Experience and/or fear of stigma from friends, partners, family (including being blame for infidelity, violence, abandonment); 2. Fear of the consequences of a positive test result. 3. Individual's endorsement of AIDS-related stigma;
	Cultural/ Gender Norms:	1. Women's lack of autonomy in making healthcare decisions.
Programmatic	**Accessibility:**	1. Lack of testing service; 2. Cost of testing; 3. Inconvenient location and hours of operation; 4. Long waiting time;
	Resources:	1. Shortage of trained counselors and health personnel; 2. Inadequate training of staff; 3. Lack of support (including emotional) for counselors; 4. Shortage of materials;
	Quality of Care:	1. Inadequate counseling rooms to protect privacy; 2. Lack of health services addressing men's needs.

Table 3 (Cont'd). Individual, Programmatic, and Societal Level Barriers to HIV Testing Reported in Low- and Middle-income Countries, 2001-2012.

Level of Organization	Theme	Barrier
Societal	**Resources**:	1. HIV-associated morbidity and mortality among healthcare workers;
	Cultural/ Gender Norms	1. Traditional masculine roles;
	Stigma/ Discrimination:	1.Community violence against people living with HIV; 2. Discrimination towards people living with HIV and its acceptance by society; 3. Negative portrayal of people living with HIV; 4. Experience and/or fear of stigma from society; 5. National- and/or local government-sponsored policies which discriminate against people living with HIV.

Table 4. Individual, Programmatic, and Societal Level Barriers to Enrollment into Pre-ART Care Reported in Low- and Middle-income Countries, 2001-2012.

Level of Organization	Theme	Barrier
Individual	**Knowledge/ Information:**	1. Unaware of HIV status due to not testing or returning for test results; 2. Lack of physical symptoms; 3. Lack of knowledge of HIV/AIDS symptoms and/or ART; 4. Fear of treatment side effects and toxicity; 5. Alcohol use;
	Accessibility:	1. Age and sex; 2. Low SES and poverty; 3. Women's low SES and lack of access to household income; 4. Inflexible work hours; 5. Distance to the clinic; 6. Perceived or actual cost of care; 7. Unfamiliarity with the hospital's system;
	Quality of Care:	1. Concerns about the quality of care at health site (e.g. protection of confidentiality, negative attitude of staff, training of staff);
	Stigma/ Discrimination:	1. Experience and/or fear of stigma/discrimination from friends, partners, family, society (including being blame for infidelity, violence, abandonment); 2. Lack of disclosure, not knowing how to and fear of potential consequences.
Programmatic	**Accessibility**:	1. Health site not accessible outside work hours;
	Quality of Care:	1. Lack of confidentiality; 2. Inadequate pre-ART services;
	Stigma/ Discrimination:	1. Attitudes and biases of healthcare workers towards people living with HIV.

Table 4 (Cont'd). Individual, Programmatic, and Societal Level Barriers to Enrollment into Pre-ART Care Reported in Low- and Middle-income Countries, 2001-2012.

Level of Organization	Theme	Barrier
Societal	**Resources:**	1. HIV-associated morbidity and mortality among healthcare workers;
	Cultural Norms:	1. Gender cultural norms (e.g. women to take care of the home); 2. Traditional masculine roles;
	Stigma/ Discrimination:	1. Community violence against people living with HIV; 2. Lack of social support in the community (e.g. neighbors, spiritual leaders); 3. Experience and/or fear of stigma; 4. National- and/or local government- sponsored policies which discriminate against people living with HIV.

Table 5. Individual, Programmatic, and Societal Level Barriers to ART Initiation Reported in Low- and Middle-income Countries, 2001-2012.

Level of Organization	Theme	Barrier
Individual	**Knowledge/ Information:**	1. Lack of physical symptoms; 2. Lack of knowledge or accurate information of ART and HIV/AIDS (fatalistic attitude, consulting solely with traditional healer, beliefs ART is harmful, misinformed of types of food that must be consumed for ART to be effective); 3. Fear of treatment side effects and toxicity; 4. Being on tuberculosis or other medical treatment;
	Accessibility:	1. Experiencing HIV-related disability; 2. Lack of employment, food insecurity, lower socioeconomic status (based on education, income, poor housing); 3. Perceived and actual financial cost of treatment including and in addition to ART (e.g. fees for consultations, medications for opportunistic infections, lab tests, loss of income due to clinic visit, more expensive treatment due to late ART initiation;); 4. Logistics (cost and access to transportation, long wait time at health site);
	Quality of Care:	1. Not receiving necessary HIV-related care (HIV/baseline CD4 test, poor/no adherence to pre-ART); 2. Negative perceptions of clinical staff (fear of stigma, poor service); 3. Changing HIV center after HIV diagnosis;
	Cultural/ Gender Norms:	1. Women's low SES and gender roles (lack of access to household income, expected to care for sick relatives);

Table 5 (Cont'd). Individual, Programmatic, and Societal Level Barriers to ART Initiation Reported in Low- and Middle-income Countries, 2001-2012.

Level of Organization	Theme	Barrier
Individual	**Stigma/ Discrimination:**	1. Experience and/or fear of stigma or discrimination from friends, partners, family (including being blame for infidelity, violence, abandonment); 2. Lack of social support and inability to cope with HIV and necessary life-changing factors; 3. Lack of disclosure and requirement to do so to access/adhere to ART; 4. Alcohol use in relatives and fear HIV status will be disclosed when under the influence; 5. Age and sex differences in disclosure, receipt of social support, and delays in enrollment into HIV care and ART initiation.
Programmatic	**Resources:**	1. High patient-provider ratio; 2. Staff burn-out due to high patient volume and work demands; 3. Staff's poor or lack of knowledge of ART; 4. Inability to properly train staff due to competing clinical demands; 5. Shortages of supplies including HIV-medications; 6. Lack of CD4 count equipment on-site;
	Quality of Care:	1. Lack of confidentiality at health site; 2. Poorly maintained clinics, including cleanliness; 3. Poor referral mechanism leading to delays between HIV diagnosis and first ART consultation; 4. Not counseling diagnosed patients on the importance of pre-ART care (e.g. treatment for opportunistic infection) and secondary transmission (including prevention of mother-to-child transmission) to keep them engaged in care; 5. Sub-optimal system to avoid losses to follow-up (LTF) among patients in pre-ART care (e.g. instructing patients in early stages of the infection to return to care months after diagnosis, lack of tracing system, healthcare workers not prioritizing retention of less advanced patients, lack of personnel training to avoid LTF);

Table 5 (Cont'd). Individual, Programmatic, and Societal Level Barriers to ART Initiation Reported in Low- and Middle-income Countries, 2001-2012.

Level of Organization	Theme	Barrier
Programmatic	**Quality of Care:**	6. Prioritizing patients with advanced disease at the expense of less advanced patients leading to long waiting time for service among the latter; 7. Strict application of policies requiring completion of adherence training before ART initiation even for patients too ill to participate and/or engage; 8. Strict application of policies requiring a "treatment buddy " before ART initiation even for patients unemployed or too poor to cover transportation cost for someone else; 9. Inconsistent application of treatment guidelines (e.g. ineligible patients treated and eligible not treated); 10. Language barrier for non-English speakers (e.g. practitioners assessing ART knowledge of Zulu speakers in English and classifying them as not ready for ART); 11. Lack of communication between counselors and physicians to address barriers to ART initiation; 12. Not instituting task shifting from physicians to nurses;
	Stigma/ Discrimination:	1. Staff's stigma/negative attitudes towards HIV patients, other staff believed to be HIV-positive, and patients of low SES
	Integration:	1. High burden of tuberculosis (TB) and lack of integration between TB, HIV and other support programs; 2. Exclusion of traditional healers; 3. Labeling/designating clinics as "HIV Clinic"; 4. Locating ART centers within larger district hospitals;
	Policies:	1. National treatment guidelines requiring advanced HIV stage to become eligible for ART; 2. Absence of treatment guidelines in the private sector.

Table 5 (Cont'd). Individual, Programmatic, and Societal Level Barriers to ART Initiation Reported in Low- and Middle-income Countries, 2001-2012.

Level of Organization	Theme	Barrier
Societal	**Resources:**	1. HIV-associated morbidity and mortality among healthcare workers;
	Knowledge/ Information:	1. Lack of knowledge or accurate information of ART and HIV/AIDS in the community (fatalistic attitude, beliefs ART causes death, cancer and infertility);
	Cultural/ Gender Norms:	1. Expectation of women to prioritize taking care of the home, traditional masculine roles, and need of women to seek permission from men for treatment;
	Stigma/ Discrimination:	1. Experience and/or fear of stigma; 2. Lack of social support in the community (e.g. neighbors, spiritual leaders); 3. National- and/or local government- sponsored policies which discriminate against people living with HIV; 4. Community violence against people living with HIV;
	Policies:	1. Lack of effective government policies/programs (e.g. South Africa's Disability Grant, user fees and cost recovery) to address unemployment, food insecurity, high prevalence of other infections, poverty; 2. Disparity in health expenditures between the private and public health sector; 3. Government policies such as the need for government-issued identification to receive ART and its effect on people living with HIV of lower SES.

Chapter 3. Does Active Screening for HIV Lead to Earlier Initiation of Antiretroviral Therapy in sub-Saharan Africa?

Introduction

The combined global effort to combat the HIV/AIDS epidemic has made tremendous progress in making antiretroviral therapy (ART) accessible to those in need. In low- and middle-income countries, where ninety-five percent of the HIV/AIDS burden is concentrated, 9.7 million people were on ART by the end of 2012 representing an unprecedented increase relative to 2002 when only 300,000 were on treatment [33]. Among these are the 7.6 million people receiving ART in sub-Saharan Africa, the region most heavily affected by HIV/AIDS [34]. The global effort has helped avert an estimated 5.5 million deaths in low- and middle-income countries since 1996, and reduced transmission of HIV by as much as 50% in some regions [15, 35] .

Despite the progress, only 35% (under 2013 World Health Organization treatment guidelines) of those in need of ART in low- and middle-income countries are receiving it [15]. Furthermore, those on treatment tend to initiate ART during the advanced, symptomatic stages of HIV disease (i.e. with a CD4 cell count below the recommended threshold for ART initiation) where the risk of morbidity and mortality are higher and opportunities to minimize transmission have been missed [5, 8, 40, 90-93]. Thus, the full potential benefits of ART are diminished [38, 39]. A key contributing factor to late ART initiation is late diagnosis of HIV [29, 88, 94-97]. Knowledge of HIV status is an essential first step to timely ART initiation [12, 13, 96, 98].

Historically, HIV testing in resource-limited countries has been delivered through Voluntary Counseling and Testing units which are poorly integrated within the healthcare system and rely on an individual's decision to seek testing [11, 51, 96]. This approach to testing combined with low perceptions of HIV-risk, fear of domestic violence and abandonment following a positive test result, high levels of stigma in the community, and limited accessibility to test units have led to underutilization of testing services [13, 50, 65, 70, 71, 99, 100]. As a consequence, only 40% of adults in sub-Saharan Africa are aware of their HIV status, and among at-risk age-groups, such as 15-24 year-olds, the proportion is as low as 15% for women and 10% for men [101]. At these levels, the likelihood of developing AIDS by the time of diagnosis and/or ART initiation increases considerably. A study in Nigeria showed that among those tested, 22.1% and 49.7% received their HIV diagnosis with advanced (CD4 cell count: 200-349 cells/μL) and severe (CD4 cell count: < 200 cells/μL) immunosuppression, respectively. This study estimated that there were at least seven years between acquisition and diagnosis of HIV infection underscoring the severity of underutilization of testing services [102].

The World Health Organization, the Joint United Nations Programme on HIV/AIDS (UNAIDS) and the US Centers for Disease Control and Prevention (CDC) support adoption of active screening to help identify and treat people living with HIV before progressing to the advanced stages of the infection [11, 16, 17, 96]. Active screening involves the routine offering of HIV testing and counseling to all individuals attending healthcare sites as part of standard care [11, 17, 96]. This approach differs from the conventional model of Voluntary Counseling and Testing in that it is integrated within the healthcare system, and relies on the provider, rather than the client, to initiate testing [11]. By making it part of standard care, active screening minimizes

stigma associated with testing, and the dependency on an individual's knowledge and risk perception to seek HIV testing [11, 17].

In addition to primary health sites, active screening has been applied in HIV-related services, such as antenatal clinics, tuberculosis clinics and clinics for sexually transmission infections, all of which serve as critical gateways or entry-points to ART [11, 17, 33, 49]. Its adoption, however, has varied across these services and with it the degree of success in identifying HIV-positive individuals [33, 49, 103-105]. For example, active screening has been successfully adopted in prevention of mother to child transmission (PMTCT) programs in antenatal clinics but its application in tuberculosis clinics, where a high proportion of patients are co-infected with HIV, has been limited [49, 50, 103, 104]. Where adopted, active screening has been well accepted by clinicians and clients, and increased both the number of patients tested per provider and the rate of identification of HIV-positive individuals [11, 13, 49-51]. Despite these benefits, studies show that a low proportion of those who test positive enroll in HIV/AIDS care and treatment sites shortly after diagnosis [11, 51, 96]. It is well-documented that after overcoming challenges to testing those who test positive, including those identified early in the infection, confront additional barriers which lead to delayed enrollment into HIV-care thus contributing to late ART initiation. These barriers range from poor referral mechanisms in the healthcare system to the inability of an individual to cope with a positive test result [65, 70, 77, 95, 96]. Therefore, we cannot assume that the documented benefits of active screening (e.g. high acceptability and identification of HIV-positive individuals) translate into initiation of treatment before the CD4 cell count drops below the recommended threshold for ART initiation.

In summary, despite successes in the scale-up of ART most patients in low- and middle-countries initiate ART late (i.e. in the advance stages of the infection where CD4 cell counts tend to be below the recommended threshold for ART initiation). Knowledge of HIV status is the first step to ART initiation. Active screening has been shown to increase the proportion of individuals aware of their HIV status but whether it leads to initiation of ART earlier (i.e. at considerably higher CD4 cell counts) in the context of limited-resource settings merits further research.

I used data from HIV care and treatment sites in sub-Saharan Africa to investigate the relationship between active screening and patient CD4 cell count at ART initiation (a measure of HIV-disease progression). I hypothesize that HIV/AIDS care and treatment sites conducting active screening initiate patients at higher CD4 cell counts compared with sites that do not. I also hypothesize that HIV/AIDS care and treatment sites receiving patients primarily from active screening entry points (e.g. antenatal clinics with Prevention of Mother to Child Transmission program) initiate patients at higher CD4 cell counts than sites whose patients come primarily from non-active screening entry points (e.g. Tuberculosis Treatment Programs, inpatient wards).

Methods

Data Source

Data for this analysis come from the International Epidemiologic Databases to Evaluate AIDS (IeDEA) (http://www.iedea-ea.org). The IeDEA initiative is a worldwide research collaboration established in 2005 to identify optimal treatment and prevention strategies across diverse economic, geographical, and cultural settings. The consortium is composed of health sites and research institutions in several countries and regions: Asia/Pacific, the Caribbean, Central and South America, Canada, the United States, West Africa, Central Africa, East Africa and Southern Africa [106]. East Africa is the region providing data for this analysis.

A site is composed of one or more clinics. To participate in the initiative, sites must 1) provide ART to HIV/AIDS patients, 2) follow patients prospectively, 3) collect data electronically, and 4) adhere to a standardized protocol for data collection. Patients aged 18 year or older at the time of ART initiation, who commenced ART between the years 2003 and 2008 were eligible for this study. Prior to analysis, the data were submitted electronically to the regional data center at Indiana University for merging and validation. Collection of these data was approved by both Indiana University's and Columbia University's Institutional Review Boards (IRBs) as well as country (Uganda's National Council on Science and Technology, Tanzania's National Institute for Medical Research) and local (Moi University's Institutional Research and Ethics Committee, Kenya Medical Research Institute, Mbarara IRB) IRBs.

Twenty-nine HIV/AIDS care and treatment sites provided routinely collected data on 45,359 patients who started ART during 2003-2008. Thirteen (0.03%) patients who had CD4 results outside the plausible range (i.e. > 1,600 cells/μL), and five (0.01%) patients whose last visit date was recorded as occurring before ART initiation were excluded. The analytical sample size was 45,341 patients from twenty-nine sites.

Patient-Level Data

Patient information was routinely collected by the site's staff where HIV/AIDS care and treatment was provided. The staff followed a standard IeDEA-prescribed protocol thus the data were standardized across sites prior to submitting to Indiana University's regional data center. Data included demographic (e.g. sex, date of birth, socio-economic status), clinical (e.g. WHO clinical stage, presence of tuberculosis disease and Kaposi's sarcoma at ART initiation), and laboratory information (e.g. CD4 cell count at ART initiation, presence of anemia at enrollment).

Site and Program-Level Data

Information on the site's characteristics and programmatic activities, including those related to the conduct of active screening and the sites' primary entry points, was collected using two structured questionnaires: the East Africa Brief Follow-up Questionnaire and the IeDEA site assessment tool (See Appendix B). Twenty-eight of the sites completed the East Africa Brief Follow-up Questionnaire and all twenty-nine sites the IeDEA Site Assessment Tool.

The East Africa Brief Follow-up Questionnaire was used to classify sites as active or non-active screening for the period 2003 to 2008. The questionnaire was utilized to collect information on factors such as 1) dates the site started providing HIV care, ART, and active screening services, 2) the population to whom active screening was offered (e.g. children, pregnant women, sex partners and/or other household members of ART patients), 3) occurrence of interruption(s) in the conduct of active screening, and 4) approaches to active screening. Data were also collected on 1) the perceived level of stigma in the site's catchment area, 2) the effect stigma may have had on uptake of HIV testing, and 3) the potential influence of Home Based Counseling and Testing on bringing subjects into care. Home Based Counseling and Testing is a form of active screening carried out outside of the site but within its catchment area. It was important to separate its potential effect on earlier initiation of ART from onsite active testing.

The IeDEA Site Assessment Tool was used to collect information on the site's physical characteristics, programmatic activities and population served. This included attributes such as 1) type of site (e.g. health center/clinic, district/provincial hospital or teaching/national referral hospital), 2) policies followed (e.g. CD4 and WHO stage criteria to start ART, charging of fees for laboratory, medication and other services), 3) resources available (e.g. number of patient beds, number and types of providers and availability, tuberculosis diagnosis and treatment), and 4) patient support services provided (e.g. adherence support, types of emotional, nutritional and pre-natal services) at the site. Additional information on the population served (e.g. urban, rural, semi-urban residents) and the primary entry points (e.g. antenatal clinics, voluntary counseling and testing units, tuberculosis clinics) referring patients to the site was also collected.

Measures

Outcome variables

The main outcome was the patient's CD4 cell count at the time of ART initiation, a measure of disease progression. The CD4 cell count measured closest to the date of ART initiation was used. CD4 measurements taken no more than six months prior to or no more than fourteen days after the start of ART were considered. CD4 cell count was analyzed as a log-transformed continuous variable in regression models to better approximate the normal distribution. CD4 values equal to 0 were changed to 1 prior to transformation.

Exposure variables

Two site-level exposure variables were used in separate analyses to assess active screening. These included whether1) a site conducted active screening and 2) if its primary sources of patient referral were entry points likely to conduct active screening. In the first analysis, sites were classified as 1) "Active" 2) "Partial" or 3) "non-Active" screening during the

2003-2008 period. The classification was based on the 1) dates provision of ART and implementation of active screening were initiated (taking into account any sustained interruption of screening services), 2) dates of patient enrollment into care (relative to when active screening was initiated), 3) approaches to active screening employed, 4) group(s) to whom active screening was offered (e.g. sex partners, children, household members of ART patients), and 5) date(s) Home Based Counseling and Testing activities took place. Sites which did not conduct active screening, initiated active screening in or after 2008 or limited screening only to children were classified as "non-Active Screening." Sites which 1) initiated active screening prior to or on the date provision of ART began, 2) started active screening prior to 2008, 3) enrolled 85% or more of their ART patients after active screening was initiated (See "Exposure Variables", Appendix A for how this percentage was calculated), and 4) offered active screening to two or more adult groups associated with ART patients (e.g. sex partner(s), other household members) were classified as "Active Screening." Lastly, sites which 1) initiated active screening after provision of ART began but prior to 2008, 2) enrolled less than 85% of their ART patients after the start of active screening, and 3) limited active screening to one adult group associated with ART patients (e.g. sex partner(s), other household members) were classified as "Partial Active Screening."

Based on information provided in the IeDEA Site Assessment Tool (See Question A15 on p.183, Appendix B), the sites were also classified as having mainly "Active Screening Entry Points" or "non-Active Screening Entry Points" in the second analysis. The classification was based on the site's primary and secondary referral sources of patients. Entry points where active screening was expected to be conducted included: Provider Initiated Testing and Counseling, Prevention of Mother to Child Transmission, and Other ("Research"). Entry points where active screening was not expected to be conducted included: Tuberculosis Clinics, In-patient Wards,

and Outpatient Wards. Voluntary Counseling and Testing units were treated as entry points where both active screening and diagnostic testing (not a form of active screening) may be conducted since these units test both subjects referred for routine testing or due to the appearance of symptoms. A site was classified as having "Active Screening Entry Points" if 1) both the primary and secondary entry points included those expected to conduct active screening, 2) one of the active screening entry points was paired with Voluntary Counseling and Testing, or 3) both the primary and secondary entry points were Voluntary Counseling and Testing units. Sites with Tuberculosis Clinic, Inpatient or Outpatient Ward as one of its entry points were classified as having "non-Active Screening Entry Points." In five instances, two distinct entry points were ranked equally for either the most (1/5) or second (4/5) most common referral source of patients. In all but one instance, the ranking did not influence the classification of the site since the entry points were concordant with regard to active screening. In the instance it did (site "EA14"), the third most common referral source of patients was used to determine the classification of the site.

Potential Confounders

Patient, programmatic and site level variables hypothesized to be common causes of the exposure and outcome variable were considered for statistical adjustment. The identification of these variables was based on a review of the HIV/AIDS literature and subject-matter knowledge.

Patient-level Variables

Patient-level variables included sex (reference group: females), age at ART initiation (reference group: ages 30-35), and year of ART initiation (reference group: 2008) [5, 80, 92, 99]. See "Potential Confounders", Appendix A for more information on these variables and other patient-level variables considered but excluded.

Programmatic-level Variables

Programmatic-level variables included presence of 1) nutritional support for all patients (reference group: absence), 2) outreach program for non-ART patients who missed visits (reference group: absence), 3) ART waiting list for eligible patients (reference group: absence), 4) tuberculosis clinic on-site (reference group: sites referring patients off-site for tuberculosis treatment), and 5) tuberculosis treatment onsite but without an onsite tuberculosis clinic (reference group: sites referring patients off-site for tuberculosis treatment) [5, 107-109]. The site's ART eligibility criteria for each World Health Organization clinical stage were also considered [110].

The ART eligibility criteria were based on the required CD4 cell count to initiate ART per World Health Organization (WHO) clinical stage (criteria for WHO stages I and II (combined), III, and IV). The CD4 thresholds used for each clinical stage were based on the cut-points reported by sites for each stage, and the WHO ART guidelines in effect during the study's follow-up period. See Potential Confounders, Appendix A for more details on this construct, and other programmatic-level variables considered but excluded.

Contextual-level Variables

Contextual variables included 1) country location (Kenya (reference group), Uganda, or Tanzania), 2) site type (health center/clinic, district/provincial hospital (reference group), or teaching/national referral hospital, 3) patient population served (mainly urban, mainly rural (reference group), and in between urban and rural), and 4) Patient-provider ratio [29, 83, 95, 111-114]. Note that due to a small number of sites located in Tanzania, country location was excluded from regression analyses but investigated as a potential confounding factor (see Sensitivity Analysis below for more how this issue was addressed). Patient-provider ratio was

divided into four categories (ratios 0-4.0, 4.01-8.5, 8.6-11.99 (reference group), and 12-35.53). See Potential Confounders, Appendix A for more details on how patient-provider ratio was calculated and other contextual variables considered but excluded.

Statistical Analysis

Data Validation and Descriptive Analysis

Standard data validation was conducted to identify potential missing and implausible values and assess the distribution of continuous variables. Descriptive statistics of key patient and contextual measures were calculated. The mean (median for non-normally distributed variables) and range are reported as measures of central tendency for continuous variables, while frequencies and proportions are reported for categorical variables.

Selection of Potential Confounders

Selection of potential confounders was completed in three steps. First, based on a review of the literature and subject-matter knowledge Directed Acyclical Graphs (DAG) hypothesizing the relationships among the main exposure, outcome and potential confounders were drawn (See Figures 4 and 5). Second, the strength and statistical significance of each bivariable association was measured (simple linear and logistic regression models, with random intercepts to account for clustering of patients within site, were used when needed) [115-118]. Lastly, variables associated (OR $\geq$ 1.20, mean CD4 count difference $\geq$ 20 cells/μL and/or P-value $\leq$ 0.10, in this instance) with at least two other variables were considered for statistical adjustment. The following variables were considered as potential confounders of the "Site Active Screening"-"Patient CD4 Cell Count at ART Initiation" relationship: 1) Site's patient-provider ratio, 2) Site's country location, 3) Site's ART eligibility criterion for WHO clinical stage I/II, and 4) Site's ART eligibility criterion for WHO clinical stage III (See Figure 6); the following were considered as potential confounders of the "Site Active Screening Entry Points"-"Patient CD4

Cell Count at ART Initiation" relationship: 1) Sex, 2) Site's patient-provider ratio, 3) Site's country location, and 4) Site's ART eligibility criterion for WHO clinical stage I/II (See Figure 7).

Multivariable Analysis

For the regression models, a log transformation of the CD4 cell count was performed to better approximate the normal distribution. Two-level mixed linear regression models were fitted with random intercepts for site to account for the correlation of patients within site (See "Justification for the use of Mixed Linear Regression Models and Assessment of Statistical Assumptions", Appendix A for more information). Two separate analyses were then performed: 1) the CD4 cell count at ART initiation for patients in "Active Screening" sites was compared with those in "Partial" or "non-Active Screening" sites (see Sensitivity Analysis below for more information), 2) the CD4 cell count at ART initiation for patients in "Active Screening Entry Points" sites was compared with those in "non-Active Screening Entry Points."

The multivariable analysis began with a bivariable model to estimate the crude association between the main exposure and outcome variable. DAG techniques as described by Greenland, Pearl, and Robins were employed to select the minimal set of potential confounders needed for adjustment [119]. Since no patient-level variable met the criteria for potential confounders, only one additional model adjusting for site level characteristics was fitted to test the association between "Active Screening" and "Patient CD4 Cell Count at ART Initiation." The site level characteristics were patient-provider ratio, ART eligibility criterion for WHO clinical stage I/II, and ART eligibility criterion for WHO clinical stage III.

In addition to the crude model, three multivariable models were fitted to test the association between "Active Screening Entry Points" and "Patient CD4 Cell Count at ART initiation." The first model adjusted only for the level-1 covariate (Sex). The second model adjusted for level-2 covariates only (patient-provider ratio, ART eligibility criterion for WHO clinical stage I/II); and the third model adjusted for both the level-1 and leve-2 covariates.

Neither the active screening nor the active screening entry points multivariable models could be adjusted for site's country location due to the small number of sites in Tanzania (n=2) and Uganda (n=4) (See sensitivity analysis for how this potential confounder was assessed). Evidence of confounding was assessed by comparing changes in the sum of the intercept and main exposure beta estimates between the crude and the final model. Presence of confounding was defined as a change of 10% or more relative to the crude estimates.

Sensitivity Analysis

Additional analyses were conducted to assess the influence of various factors on study conclusions. I calculated and compared the median time from patient enrollment into care until initiation of ART for active and non-active screening sites to assess whether the potential benefits of screening were negated by programmatic delays in treatment initiation. Approximately 17% of patients were missing CD4 cell count at ART initiation and thus did not contribute to the model results. I compared the distribution of sex, and age and WHO clinical stage at ART initiation for patients with and without CD4 cell counts at ART initiation and assessed differences. To assess the effect of not adjusting for country location, the final models were re-fitted limiting the data to sites in Kenya which accounted for 79% and 74% of sites and patients, respectively. To assess the potential influence of patient socio-economic status, which was not adjusted due to large number of missing values, appropriate measures of socioeconomic

status for East Africa (e.g. level of education, availability of electricity and piped water in the home) were added to the hypothesized DAGs. I then assessed the need to adjust for these measures socio-economic status by determining the minimal set of variables needed to address confounding. Lastly, to assess the potential impact of classifying the six "Partial Active Screening" sites (EA04, EA05, EA10, EA12, EA13, and EA33) as "non-Active Screening", the active screening final model was fitted under two scenarios. In the first scenario, patients who enrolled into care prior to the initiation of active screening were excluded from "Partial Active Screening" sites EA04, EA05, EA10, and EA13 and these sites were reclassified as "Active Screening" sites. Since sites EA12 and EA33 were classified as "Partially" because active screening was limited to sex partners of ART patients, the classification for these sites remained as "non-Active Screening." In the second scenario, all six "Partial Active Screening" were excluded from the analysis. The conclusions based on these scenarios were compared with those reached with the final active screening model. All analyses were performed in SAS® Version 9.2.

Results

Patient and Contextual Characteristics of Study Population

Table 1 shows that most of the 45,341 patients initiated ART in Kenya, which accounted for 33,586 (74%) patients in 23 (79%) sites, followed by Uganda with 9,737 (21%) patients in 4 (14%) sites, and Tanzania with 2,018 (4%) patients in 2 (7%) sites. Patients predominantly received care in teaching/national referral hospitals (40.9%) and district/provincial hospital (38.0%). The percentage of patients initiated on ART increased each year until 2008 with the largest increases in earlier years. The median age at the start of ART was 37 years (range 18 to 88 years), and 64.3% were female. Eighty-three percent of patients had a CD4 cell count at ART initiation, and the mean value was 87.2 cells/μL.

As shown in Table 2, the total number of patients initiated on treatment during the six-year period ranged from 55 to 8,592 among the twenty-nine sites. The variation was partly due to differences in the number of years sites have been providing ART. The patient median age per site ranged from 21 to 40 years, and at each site more than half of the patients were women (range 58.7-100%).

Figure 1 shows the variation in the crude mean patient CD4 cell count and the proportion of patients missing CD4 cell count at ART initiation by site. The crude patient mean CD4 cell count was 87.2 cells/μL (site range: 71.6 to 196.1 cells/μL). The percent missing CD4 cell count varied widely among sites ranging from 1% to 70% (mean 16.5%).

Association between Active Screening and CD4 Cell Count at ART Initiation

Table 3 lists the classification of each site by active screening. One site (3.4%) did not provide information on active screening. Twelve of the twenty-eight sites (42.8%) that responded to the follow-up questionnaire were classified as "Active Screening." The majority of ART patients (88% - 100%) at these sites enrolled into care after active screening practices were implemented. The most common approach to HIV screening among these sites was Provider Initiated Testing and Counseling (11/12 or 91.7% of sites), followed by Prevention of Mother to Child Transmission (8/12 or 66.7% of sites) and Prevention with Positives (5/12 or 41.7). With the exception of two sites, which offered treatment to two adult groups, all "Active Screening" sites offered testing to relatives, sex partner(s), other household members, and children of ART patients.

Ten of the twenty-eight sites (35.7%) were classified as "non-Active Screening." With the exception of one site (EA34), none of the ART patients at these sites was exposed to active screening at the site since all were enrolled into care before active screening practices were implemented. For site EA34, 2.4% of patients enrolled into care after active screening was initiated at this site. Among the six sites classified as "Partial" (21.4%), two had 90% or more of their patients enrolled into care after active screening practices began. However, these sites limited active screening to sex partner(s) of ART patient making it unlikely that a high percentage of the total patient population was actively screened for HIV. For the other four sites, between 27.7% and 68.7% of patients enrolled into care after active screening began at the site. As described above, "Partial" and "non-Active Screening" sites were combined in the analysis. Lastly, Home Based Counseling and Testing was performed in 2007 in the catchment area of one

study site and was reported as a contributor to increased demand for secondary testing. No other site performed Home Based Counseling and Testing between 2003 and 2008.

Figures 2A and 2B show the crude mean patient CD4 cell counts at ART initiation for each site stratified by active screening. The crude mean patient CD4 cell count at ART initiation were 89.7 (range: 77.7 to 170.5) and 85.6 (range: 71.6to 196.1) cells/μL for active and non-active screening sites, respectively. The site- and programmatic-level variables selected for statistical adjustment and their respective association with the exposure and outcome are listed in Table 4. Relative to non-Active Screening sites, sites conducting active screening were more likely to have sites with the lowest (0.0-4.0) and highest (12.0-35.5) patient-provider ratios, and an ART guideline requiring a CD4 below 350 cells/μL to initiate ART for patients in WHO clinical stage III. Conversely, they were less likely to have sites with the second lowest patient-provider ratio (4.01-8.5) and an ART guideline requiring a CD4 below 200 cells/μL to initiate ART for patients in WHO clinical stages I or II.

Table 5 presents estimates for the crude and adjusted random effects models. In accordance with Figures 2A and 2B, the crude mean CD4 cell count for active and non-active screening sites were similar (99.8 vs. 98.7; p-value 0.91). After adjusting for contextual potential confounders (patient-provider ratio, ART eligibility criterion for WHO clinical stage I/II, and ART eligibility criterion for WHO clinical stage III), the mean CD4 cell count for Active Screening sites was 92.6 cells/μL compared with 95.5 cells/μL (p-value 0.76) for non-Active Screening sites. Estimates for these models in the log scale are presented in "Results", Appendix A.

Association between Active Screening Entry-Points and CD4 Cell Count at ART Initiation

Table 6 lists the primary and secondary source of patients and "Active Screening Entry Point" classification for each site. Of the twenty-nine sites, twenty-two (75.9%) were classified as having primarily "Active Screening Entry Points" and seven (24.1%) were classified as having primarily "non-Active Screening Entry Points." Among "Active Screening Entry Points" sites, the most common primary or secondary entry point was Voluntary Counseling and Testing unit (24/44 or 54.5%) followed by Provider Initiated Testing and Counseling (11/44 or 25.0%) and Prevention of Mother to Child Transmission (9/44 or 20.5%). Among "non-Active Screening Entry Points" sites, the most common entry point was In-patient Ward (5/14 or 35.7%) followed by Provider Initiated Testing and Counseling (3/14 or 21.4%), and a tie between Outpatient Ward and Voluntary Counseling and Testing (2/14 sites or 14.3% for each).

Figures 3A and 3B show the crude mean patient CD4 cell count at ART initiation for each site stratified by Active Screening Entry Points. The crude mean patient CD4 cell count at ART initiation were 93.3 (range: 77.7 to 196.1) and 80.1 (range: 71.6 to 124.5) cells/μL for sites with Active and non-Active Screening Entry Points, respectively. As shown in Table 7, sites with Active Screening Entry Points were less likely to have male patients and the second highest (4.01-8.5) patient-provider ratios. They were also more likely to have sites with the lowest patient-provider ratios (0.0-4.0) and follow an ART guideline requiring a CD4 below 200 cells/μL to initiate ART for patients in WHO clinical stages I or II.

Table 8 presents the four random effects models fitted. Similarly to Figures 3A and 3B, the crude model estimated a higher mean CD4 cell count for patients in "Active Screening Entry-Points" sites relative to "non-Active Screening Entry-Points" (104.6 vs. 84.9; p-value 0.03).

Adjusting for sex (Model 2) did not materially change the mean difference in CD4 cell counts (19.7 cells/μL vs. 19.6 cells/μL). After adjusting for contextual and programmatic factors (patient-provider ratio, ART eligibility criterion for WHO clinical stage I/II) in Model 3, the mean difference between Active and non-Active Screening Entry Points sites increased to 23.5 cells/μL (110.41 vs 86.9; p-value 0.004). A similar mean difference is estimated in final Model 4 (118.2 vs 94.5 or 23.7 cells/μL; p-value 0.005) which adjusts for patient, programmatic and contextual factors (sex, ART eligibility criterion for WHO clinical stage I/II, patient-provider ratio). Estimates for these models on the log scale are presented in "Results", Appendix A.

Sensitivity Analysis

The median time to ART initiation after enrolling into care was the same among Active and non-Active Screening sites (Active Screening Site Median (IQR): 56 days (21-140); non-Active Screening Sites: 56 days (19-167)). Patients with and without a CD4 cell count at ART initiation were similar with respect to sex, WHO clinical stage and age at ART initiation. Limiting the data to sites in Kenya led to similar results and thus did not change study conclusions. I hypothesized that patient socioeconomic status would be associated with the main exposure and outcome only indirectly via potential confounders site patient-provider ratio (active screening and active screening entry point models) and sex (active screening entry point model). Since these factors were adjusted in the final models, it is unlikely that lack of adjustment for socio-economic status influenced study conclusions. Similarly, neither the exclusion of "Partial" sites nor the re-classification of four of these sites to "Active Screening" changed study conclusions. The results of these analyses are presented in Tables 11 – 15 under "Sensitivity Analysis", Appendix A.

Discussion

Our results show that when implemented in HIV-related programs (i.e. entry-points such as Prevention of Mother to Child Transmission), active screening is associated with earlier initiation of ART. The mean CD4 cell count for patients in sites with predominantly "Active Screening Entry Points" (e.g. Provider Initiated Testing and Counseling, Prevention of Mother to Child Transmission) was, on average, 24 cells/μL higher (118.2 cells/μL vs. 94.5; p-value 0.005) compared with patients in "non-Active Screening Entry Points" sites (e.g. Tuberculosis Clinics, In-patient Wards). This modest increase may translate into better health outcomes, including improved survival, for these patients. Furthermore, this increase may lead to greater benefit for patients with the lowest CD4 cell counts given the shift in the CD4 cell count distribution that would result from higher population mean CD4 values. Therefore, the greatest impact of active screening may be on the most vulnerable patients (i.e. those with the lowest CD4 cell counts).

Our findings are in line with the limited number of studies testing the association between active screening and CD4 cell count at ART initiation in low- and middle-income countries. A study using data from Latin America, Asia and countries throughout sub-Saharan Africa showed that patients likely to have been screened for HIV had a mean CD4 cell count at ART initiation that was 30 cells/μL higher than those unlikely screened [99]. A South African study assessing the impact of provider-initiated testing on HIV-associated tuberculosis patients also found that screening was associated with a mean CD4 cell count 24 cells/μL higher at ART initiation [49]. Wachira et al study in Kenya measured a mean CD4 cell count of 190 cells/μL and 136 cells/μL for patients referred from provider-initiated testing and tuberculosis clinics, respectively [120]. Similarly to our findings despite implementation of active screening, patients in these studies had a mean CD4 cell count at ART initiation well-below 200 cells/μL and thus, on average, initiated

ART late. In a study in Haiti, the mean patient CD4 cell count at ART initiation for patients actively screened was 351 cells/μL [121]. This study lacked a comparison group and therefore we cannot confidently associate these results with active screening. However, the mean CD4 cell count is well-above what typical values observed in resource-limited settings.

A number of factors may explain why we were not able to detect a statistical difference in mean CD4 cell counts at ART initiation (92.6 cells/μL vs 95.5 cells/μL; p-value 0.76) when active screening was implemented in HIV/AIDS care and treatment sites. First, the literature shows that HIV-positive individuals in sub-Saharan Africa face multiple barriers (e.g. low socioeconomic status, overcrowded sites, physical accessibility of the site) at multiple levels (personal, site, and contextual, respectively) all of which can contribute to late ART initiation following a positive diagnosis [71, 89, 95]. It is possible that individuals diagnosed at active screening sites may have been diagnosed earlier in the infection but due to barriers to ART initiation started treatment as late as individuals diagnosed later in non-active screening sites. However, the analysis accounted for individual, site and contextual-level characteristics which to some extent correlate with barriers to ART initiation. Furthermore, the median time to ART initiation relative to enrollment into care did not differ between active and non-active screening sites (See "Sensitivity Analysis", Appendix A). Nonetheless, other factors outside these areas (e.g. lack of transportation or access to existing modes of transportation, HIV-related stigma) were not considered.

The grouping of "Partial" and "non-Active Screening" sites and the conduct of Home Based Counseling and Testing in the site's catchment area may have raised the mean CD4 cell count of patients in "non-Active Screening" sites making it more similar to that of "Active Screening" sites. As a consequence, these factors may have masked a true difference in patient

CD4 cell count between active and non-active screening sites. As shown in Table 3, although the percent was not as high as that of "Active Screening" sites, "Partial Active Screening" sites had a considerable number of patients enrolling into care after initiation of their active screening program, and thus likely exposed to screening. Despite the percentages, neither the reclassification of four of the six "Partial" sites as "Active Screening", following the removal of patients enrolled prior to initiation of active screening, nor the exclusion of all 'Partial" sites changed study conclusions. The conduct of Home Based Counseling and Testing in the sites' catchment area was not a factor during the 2003-2008 period with the notable exception of one site. This site (EA16), however, was an active screening site for the entire period of follow-up.

Misclassification of sites by active screening status may have introduced bias. The classification was largely based on recollection which is prone to recall bias. The bias would have been non-differential and thus may explain the null findings for the Active Screening analysis (note that the Active Screening Entry Point classification was based on the most common sources of HIV patients which is less likely to be prone to recall bias). Lastly, our findings may be due to the manner active screening is implemented in these two types of healthcare settings. In HIV/AIDS care and treatment sites, active screening relies on ART patients to disclose their HIV status to sex partner(s), relatives or other adults household members and also convince them to get tested. HIV-positive individuals in low- and middle-income countries face multiple barriers to disclosure perhaps limiting the potential benefits of active screening [64, 70]. Furthermore, HIV-related stigma may prevent individuals from visiting a health site dedicated solely for the treatment of HIV/AIDS even if disclosure is not an issue [57]. At entry points (Prevention of Mother to Child Transmission) on the other hand, healthcare providers communicate directly with their target population and this may be more

effective in accepting HIV testing. Though we do not know what proportion of the sites' patient population was screened, the literature suggests that the proportion screened in sites is likely less than that screened at entry points such as antenatal clinics [96, 122-124]. In addition, a portion of HIV positive individuals being tested for HIV in active screening sites may have done so out of personal concerns or the behest of a provider after the appearance of HIV-related symptoms. In this scenario, HIV testing constitutes diagnostic testing rather than active screening. Though this scenario may also occur in entry-points (e.g. outpatient ward), it is unlikely to be as common among entry points like Prevention of Mother to Child Transmission programs, where HIV-positive individuals tend to be younger, and asymptomatic and therefore at earlier stages of the infection [125]. Therefore, although both the site and the entry point presented in this scenario are conducting active screening, the degree of penetration of active screening differs and consequently the impact on CD4 cell count at ART initiation.

There are some limitations to this study. Nearly seventeen percent of the patients were missing a CD4 cell count at ART initiation and therefore were systematically excluded from multi-level models. These patients, however, were similar to those with CD4 cell counts with regard to sex, age and WHO clinical status at ART initiation, a marker of disease progression. The programmatic and site level data collected through the IeDEA Site Assessment Tool reflects information at one point in time which may not fully reflect conditions during the entire follow-up period. Other unmeasured patient factors may have affected our results. However, individual, site and contextual-level factors were considered during the analysis and adjusted as needed. In addition, the potential influence of patient socio-economic status, a prominent unmeasured variable, was considered during our sensitivity analysis and it is unlikely that this factor would change our study conclusions.

This study has several strengths. The data included a respectable number of sites all with a considerable number of patients initiating treatment. The sites were from diverse geographic settings and data collection extended over several years. Although most of the sites and patients came from Kenya, the findings likely apply to resource-limited settings with a generalized HIV epidemic. The classification of the sites with regard to active screening was based on a host of factors (including qualitative data) assessing the HIV testing experience at the site and its catchment area during the follow-up period. The completeness of the data was high for all the variables considered and/or adjusted in the models. Individual, programmatic and site level were adjusted and/or considered for adjustment in multilevel models which is uncommon in these types of studies. Finally, given the nature of the data collection (e.g. not from a cohort study with inclusion/exclusion criteria) our results represent real world conditions under which patients access and receive care. The results are generalizable to resource-limited settings with sub-optimal health-care systems and a generalized HIV epidemic.

Conclusions

Late ART initiation threatens the effectiveness of ART in reducing morbidity, mortality and HIV transmission [38, 39]. Active screening has been adopted by most low- and middle-income countries to identify people living with HIV and bring them into care before progressing to the advanced stages of the infection [96]. Similar to other studies, our analyses show that implementation of active screening is associated with higher CD4 cell counts at ART initiation in resource-limited settings [49, 99, 120]. This increase may translate into lower morbidity and mortality especially for those patients with the lowest CD4 cell counts who may benefit most from the shift in the CD4 cell count distribution resulting from higher population CD4 cell means. Our results also show that additional interventions would be needed (e.g. home-based counseling and testing) to combat late ART initiation since active screening alone has not been shown to increase CD4 cell values to levels sufficient to prevent late ART initiation. Future research should investigate 1) the average CD4 cell count at the time of HIV diagnosis particularly for screened patients to help determine the impact other factors may have in limiting the benefits of active screening, and 2) whether active screening results in improved survival for ART patients.

Tables and Figures

Active Screening – CD4 Cell Count at ART Initiation

Table 1. Distribution, Key Demographic and Clinical Characteristics of Patients Initiating Antiretroviral Treatment 2003 to 2008 in the 29 Sites in East Africa.

	No. (% or Min-Max)
Patient Population by Country	
Kenya	33,586 (74.1)
Uganda	9,737 (21.5)
Tanzania	2,018 (4.4)
Patient Population by Site Type	
Health Center/Clinic	9,539 (21.0)
District/Provincial Hospital	17,244 (38.0)
Teaching/National Referral Hospital	18,558 (40.9)
Patient by Year of ART Initiation	
2003	689 (1.5)
2004	3,012 (6.6)
2005	9,169 (20.2)
2006	10,931 (24.1)
2007	12,776 (28.2)
2008	8,764 (19.3)
Median Age at ART Initiation	37 (18-88)
Female Patients	29,118 (64.3)
Patients with a CD4 Cell Count at ART Initiation	37,864 (83.5)
Mean Patient CD4 Cell Count at ART Initiation (cells/μL)	87.2 (0-1598.7)

Table 2. Key Characteristics of the 29 Sites in East Africa and Attributes of their Respective Patient Population.

Site (N=29)	Country	Site Type	Population Served	ǂNo. of ART Patients (N=47,518)	Year of ART Initiation	Median Age at ART Initiation	Percent Female
EA01	Kenya	District/ Provincial Hospital	In-between Urban/rural	3993	2003-2008	36 (18-88)	66.0
EA02	Kenya	Health Center/Clinic	Mainly Urban	172	2007-2008	35 (20-69)	62.9
EA03	Kenya	Health Center/Clinic	Mainly Urban	94	2007-2008	29 (19-49)	100.0
EA04	Kenya	Teaching/ National Referral Hospital	Mainly Urban	8592	2003-2008	37 (18-81)	58.7
EA05	Kenya	District/Provincial Hospital	In-between Urban/rural	324	2005-2008	39 (19-70)	73.2
EA06	Kenya	District/Provincial Hospital	In-between Urban/rural	583	2006-2008	38 (20-75)	66.6
EA07	Kenya	District/Provincial Hospital	In-between Urban/rural	322	2006-2008	38 (19-61)	66.2
EA08	Kenya	District/Provincial Hospital	In-between Urban/rural	788	2004-2008	37 (19-79)	65.5

Note: ǂNumber of patients who started ART by Dec. 2008

Table 2 (Cont'd). Key Characteristics of the 29 Sites in East Africa and Attributes of their Respective Patient Population.

Site (N=29)	Country	Site Type	Population Served	ǂNo. of ART Patients (N=47,518)	Year of ART Initiation	Median Age at ART Initiation	Percent Female
EA09	Kenya	District/Provincial Hospital	Mainly Urban	2023	2004-2008	38 (18-74)	70.0
EA10	Kenya	Health Center/Clinic	Mainly Rural	891	2007-2008	38 (20-78)	65.5
EA11	Kenya	Health Center/Clinic	In-between Urban/rural	2004	2004-2008	38 (18-75)	65.1
EA12	Kenya	Health Center/Clinic	Mainly Rural	788	2004-2008	38 (19-77)	62.4
EA13	Kenya	District/Provincial Hospital	Mainly Urban	2443	2006-2008	37 (18-81)	64.5
EA14	Kenya	District/Provincial Hospital	Mainly Urban	142	2007-2008	35 (20-62)	64.1
EA15	Kenya	Health Center/Clinic	In-between Urban/rural	1343	2004-2008	37 (19-76)	66.8
EA16	Kenya	Health Center/Clinic	Mainly Urban	2781	2003-2008	38 (18-76)	64.7

Note: ǂNumber of patients who started ART by Dec. 2008

Table 2 (Cont'd). Key Characteristics of the 29 Sites in East Africa and Attributes of their Respective Patient Population.

Site (N=29)	Country	Site Type	Population Served	ǂNo. of ART Patients (N=47,518)	Year of ART Initiation	Median Age at ART Initiation	Percent Female
EA17	Kenya	District/Provincial Hospital	Mainly Urban	2933	2005-2008	38 (18-80)	68.1
EA18	Kenya	District/Provincial Hospital	In-between Urban/rural	538	2005-2008	36 (19-77)	62.5
EA19	Kenya	Health Center/Clinic	Mainly Urban	782	2007-2008	33 (18-72)	66.8
EA20	Kenya	Health Center/Clinic	Mainly Urban	55	2007-2008	21 (18-25)	77.1
EA21	Kenya	District/Provincial Hospital	In-between Urban/rural	1080	2006-2008	36 (18-77)	62.6
EA22	Kenya	Health Center/Clinic	Mainly Rural	629	2004-2008	38 (18-78)	68.8
EA23	Kenya	District/Provincial Hospital	Mainly Urban	286	2003-2008	30 (18-57)	73.4
EA27	Tanzania	Teaching/National Referral Hospital	Mainly Urban	607	2005-2008	40 (18-82)	61.0

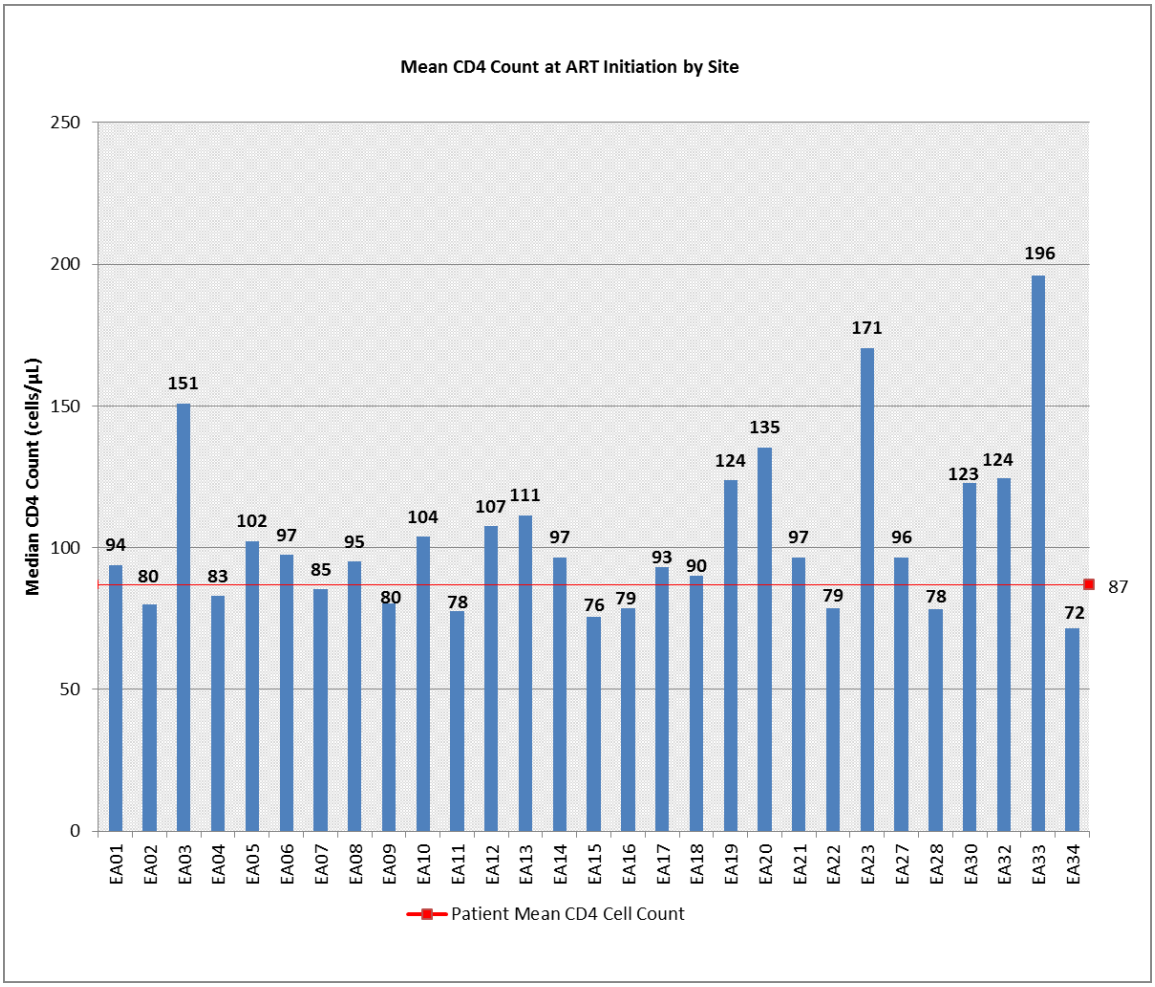
Note: ǂNumber of patients who started ART by Dec. 2008

Table 2 (Cont'd). Key Characteristics of the 29 Sites in East Africa and Attributes of their Respective Patient Population.

Site (N=29)	Country	Site Type	Population Served	ǂNo. of ART Patients (N=47,518)	Year of ART Initiation	Median Age at ART Initiation	Percent Female
EA28	Tanzania	District/Provincial Hospital	Mainly Urban	1411	2005-2008	38 (19-82)	65.4
EA30	Uganda	Teaching/National Referral Hospital	Mainly Urban	339	2003-2008	32 (18-52)	69.6
EA32	Uganda	Teaching/National Referral Hospital	Mainly Rural	1363	2007-2008	35 (18-80)	60.5
EA33	Uganda	District/Provincial Hospital	Mainly Urban	378	2003-2008	32 (19-71)	68.8
EA34	Uganda	Teaching/National Referral Hospital	Mainly Urban	7657	2003-2008	36 (18-80)	64.2

Note: ǂNumber of patients who started ART by Dec. 2008

Figure 1. Crude Mean CD4 Count at ART Initiation of Patients Initiating Antiretroviral Therapy 2003-2008 in the 29 Sites in East Africa.



Facility	EA01	EA02	EA03	EA04	EA05	EA06	EA07	EA08	EA09	EA10	EA11	EA12
No. Patients	3993	172	94	8592	324	583	322	788	2023	891	2004	788
% Missing CD4	15.3	2.9	1.1	14.1	19.1	13.2	9.6	11.8	13.1	23.1	11.7	12.1

Facility	EA13	EA14	EA15	EA16	EA17	EA18	EA19	EA20	EA21	EA22	EA23	EA27
No. Patients	2443	142	1343	2781	2933	538	782	55	1080	629	286	607
% Missing CD4	15.8	15.5	14.5	13.6	14.4	15.2	3.1	1.8	17.5	12.9	39.5	8.6

Facility	EA28	EA30	EA32	EA33	EA34	Total
No. Patients	1411	339	1363	378	7657	45341
% Missing CD4	16.0	13.3	29.7	69.6	22.3	16.5

Table 3. Active Screening Characteristics and Classification During 2003-2008 for the 29 Sites in East Africa.

[1]Site (N=29)	[2]Date Provision of ART Initiated	Date Active Screening Initiated	Earliest Year of Enrollment; (Percentage of ART Patients Enrolled After Initiation of Active Screening); No. ART Patients	[3]HIV Testing Method Reported (Time Provided: E: At Enrollment, FU: During Follow-up, B: Both E and FU)	Population Offered Active Screening				[4]Active Screening Classification 2003-2008
					Relatives	Sex Partner	Other Household Adults	Children	
EA01	99/2004	07/2004	2002; (97.2); 3993	PITC (B), PMTCT (B), HBCT(B)	✓	✓	✓	✓	Yes
EA02	05/2007	99/2007	2007; (95.9); 172	AD (B), PITC (B), FTA(B), PI (B)	✓	✓	x	✓	Yes
EA03	99/2006	99/2008	2002; (0); 94	PMTCT (B), FTA (B)	x	x	x	✓	No
EA04	11/2001	99/2005	2001; (68.7); 8592	HBCT(E), PITC (B), PWP (E), TP (B)	✓	✓	✓	✓	*Partial
EA05	11/2005	99/2006	2002; (68.2); 324	PITC (E), HBCT (E), PMTCT (B)	✓	✓	✓	✓	*Partial
EA06	03/2006	99/2010	2003; (0); 583	PITC (B), HBCT (E), PMTCT (B), PWP (B)	✓	✓	✓	✓	No
EA07	03/2006	99/2010	2005; (0); 322	PITC (E), VCT (B), HBCT (B), PMTCT (B)	x	✓	x	✓	No
EA08	11/2004	99/2009	2002; (0); 788	PITC (B), HBCT (B), PWP (B), PMTCT (B)	✓	✓	✓	✓	No
EA09	08/2004	08/2004	2002; (93.9); 2023	PITC (E), PWP (B), TP (B), PMTCT (B)	✓	✓	✓	✓	Yes
EA10	99/2007	99/2007	2005; (46.4); 891	VCT (E), PMTCT (B), HBCT (E)	✓	✓	✓	✓	*Partial
EA11	99/2004	99/2004	2003; (94.0); 2004	PITC (E), PMTCT (B), HBCT (E), PWP (F)	✓	✓	✓	✓	Yes
EA12	07/2004	07/2004	2002; (95.0); 788	PITC (B), VCT (E), HBCT (B), PMTCT (B)	x	✓	x	✓	Partial
EA13	99/2006	99/2007	2003; (27.7); 2443	PITC (B), HBCT (B), PMTCT (B), PWP (B)	✓	✓	✓	✓	*Partial
EA14	10/2007	99/2003	2005; (100); 142	PITC (E), PMTCT (B), VCT (E)	x	✓	✓	✓	Yes

Notes:[1]29 sites complete IeDEA Site Assessment Tool; 28 sites completed the East Africa Brief Follow-up Questionnaire.
[2]"99" signifies that month was not reported. "N/A" signifies not available.
[3]PITC= Provider Initiated Testing and Counseling, PMTCT= Prevention of Mother to Child Transmission, HBCT=Home Based Counseling and Testing, AD=Assisted Disclosure, FTA=Family Table Assessment, PI=Partner Involvement, PWP=Prevention with Positive, TP=Testing Partners, VCT=Voluntary Counseling and Testing, PEDs=Pediatric Clubs, CT=Children Testing
[4]"Partial" were combined with "non-Active Screening" in the analysis.
*Site was re-classified as "Active Screening" in sensitivity analysis after excluding patients enrolled into care prior to initiation of active screening.

Table 3 (Cont'd). Active Screening Characteristics and Classification During 2003-2008 for the 29 Sites in East Africa.

[1]Site (N=29)	[2]Date Provision of ART Initiated	Date Active Screening Initiated	Earliest Year of Enrollment; (Percentage of ART Patients Enrolled After Initiation of Active Screening); No. ART Patients	[3]HIV Testing Method Reported (Time Provided: E: At Enrollment, FU: During Follow-up, B: Both E and FU)	Population Offered Active Screening				[4]Active Screening Classification 2003-2008
					Relatives	Sex Partner	Other Household Adults	Children	
EA15	99/2004	99/2010	2002; (0); 1343	PITC (E), VCT (B), HBCT (B), PMTCT (B)	x	✓	x	✓	No
EA16	11/2001	11/2001	2001; (100); 2781	PITC (B), PMTCT (B), PWP (B), HBCT (E)	✓	✓	✓	✓	Yes
EA17	12/2005	12/2005	2001; (92.5); 2933	PITC (E), PWP (B), PMTCT (B), HBCT (B)	✓	✓	✓	✓	Yes
EA18	N/A	N/A	N/A	N/A	N/A				N/A
EA19	04/2005	03/2005	2000; (99.9); 782	AD (B), PITC (B), FTA (B)	✓	✓	✓	✓	Yes
EA20	12/2005	12/2005	2006; (100); 55	PITC (E), VCT (E), HBCT (F)	✓	✓	✓	✓	Yes
EA21	08/2006	08/2006	2006; (97.5); 1080	PITC (B), HBCT (E), PWP (B), PMTCT (B)	✓	✓	✓	✓	Yes
EA22	7/2004	99/2009	2002; (0); 629	PITC (E), PMTCT (F), PWP (B), HBCT (E)	✓	✓	✓	✓	No
EA23	99/2004	12/2003	2003; (87.8); 286	VCT (E), PITC (E), PMTCT (B)	✓	✓	✓	✓	Yes
EA27	07/2005	99/2010	2005; (0); 607	PITC (B), TP (B), PWP (B)	✓	✓	x	✓	No
EA28	06/2005	07/2009	2005; (0); 1411	FTA (B), PEDs (B)	✓	✓	x	✓	No
EA30	04/2003	99/2003	2003; (92.3); 339	TP (B), CT (B)	✓	✓	✓	✓	Yes
EA32	99/2002	Not Provided	Screening Not Provided; (0); 1363	No method used	N/A				No
EA33	99/1998	99/2003	2003; (92.9); 378	TP (B)	x	✓	x	✓	Partial
EA34	99/2004	99/2008	2002; (2.4); 7657	TP (B)	x	✓	x	✓	No

Notes: [1]29 sites complete IeDEA Site Assessment Tool; 28 sites completed the East Africa Brief Follow-up Questionnaire.

[2]"99" signifies that month was not reported. "N/A" signifies not available.

[3]PITC= Provider Initiated Testing and Counseling, PMTCT= Prevention of Mother to Child Transmission, HBCT=Home Based Counseling and Testing, AD=Assisted Disclosure, FTA=Family Table Assessment, PI=Partner Involvement, PWP=Prevention with Positive, TP=Testing Partners, VCT=Voluntary Counseling and Testing, PEDs=Pediatric Clubs, CT=Children Testing

[4]"Partial" were combined with "non-Active Screening" in the analysis.

Figure 2A. Crude Mean CD4 Count at ART Initiation for Sites Conducting Active Screening 2003-2008 in East Africa.

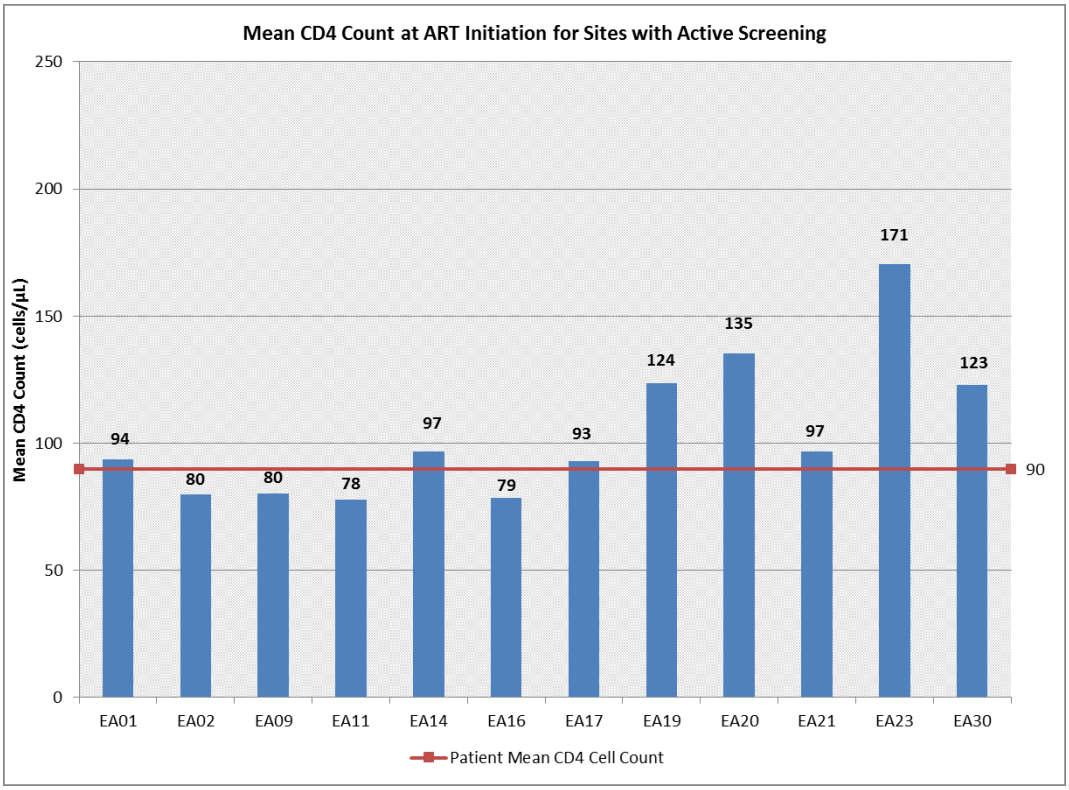


Figure 2B. Crude Mean CD4 Count at ART Initiation for Sites not Conducting Active Screening 2003-2008 in East Africa.

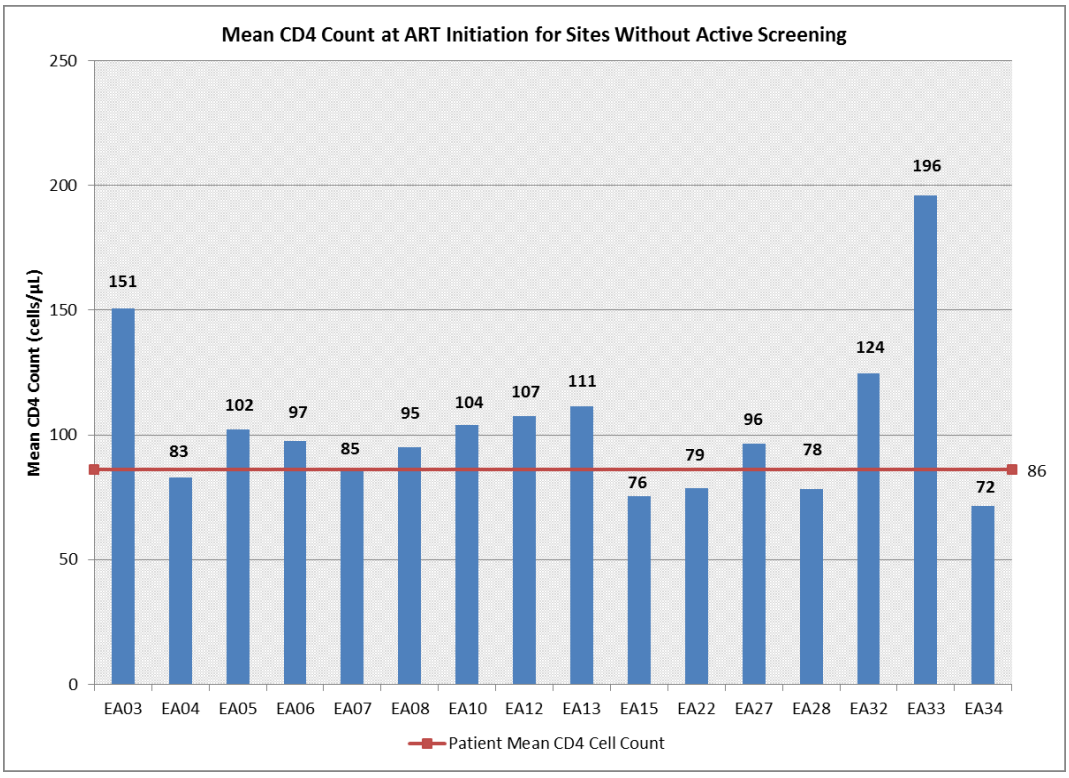


Table 4. Distribution of Potential Confounders and Associations with the Active Screening (Exposure) and Patient CD4 Cell Count at ART Initiation (Outcome).

	Sites with Active Screening	Sites without Active Screening	Association with the Exposure	Association with the Outcome
	N (%)	N (%)	OR (P-value[1])	Mean CD4 Difference (P-value)
Site and Programmatic-level Level Characteristics				
Number of Sites	12 (100)	16 (100)	--	--
Site Patient-Provider Ratio				
0.0 to 4.0	5 (41.7)	1 (6.3)	15.0 (0.10)	+33.3 (0.01)
4.01 to 8.5	1 (8.3)	6 (37.5)	0.5 (1.00)	+21.1 (0.04)
8.6 to 11.99	2 (16.7)	6 (37.5)	Reference	Reference
12.0 to 35.53	4 (33.3)	3 (18.8)	4.0 (0.31)	-1.7 (0.85)
Site's ART Eligibility Criterion for Patients in WHO Clinical Stage 1 or 2 (<200 vs 200+ cells/μL)	7 (58.3)	13 (81.3))	0.32 (0.23)	-23.0 (0.03)
Site's ART Eligibility Criterion for Patients in WHO Clinical Stage 3 (<350 vs 350+ cells/μL)	4 (33.3)	4 (25.0)	1.22 (1.00)	-20.3 (0.05)

[1]Fisher's Exact Test used due to expected cell values < 5.

Table 5. Mean CD4 Values for Crude and Adjusted Mixed Model Comparing Patients in Sites with and without Active Screening.

Parameter	Model 1: Crude Mean CD4 (P-Value)	Model 2: Adjusted Mean CD4 (P-Value)
Active Screening		
Yes	99.8 (0.91)	92.6 (0.76)
No	98.7 (ref)	95.5 (ref)
Site Patient-Provider Ratio		
0-4.0	---	128.9 (0.11)
4.01-8.5	---	119.6 (0.07)
8.6-11.99	---	95.5 (ref)
12-35.33	---	93.3 (0.83)
Site ART Eligibility Criteria for Patients in WHO Clinical Stage 1 or 2		
< 200 cells/μL	---	89.1 (0.61)
200+ cells/μL	---	95.5 (ref)
Site ART Eligibility Criteria for Patients in WHO Clinical Stage 1 or 2		
< 350 cells/μL	---	93.0 (0.84)
350+ cells/μL	---	95.5 (ref)

Table 6. Classification of the 29 Sites by Active Screening Entry Points based on Primary and Secondary Source of Patients.

Site (N=29)	Primary Source of Patients	Secondary Source of Patients	Site has Primarily Active Screening Entry Points
EA01	Provider Initiated Testing and Counseling	Voluntary Counseling and Testing (directly)	Yes
EA02	Voluntary Counseling and Testing (via Referral)	Voluntary Counseling and Testing (directly)/Other (Transfer In) [tied]	Yes
EA03	Voluntary Counseling and Testing (directly) and (via Referral)[tied]	Provider Initiated Testing and Counseling	Yes
EA04	Provider Initiated Testing and Counseling	Inpatient Wards	No
EA05	Provider Initiated Testing and Counseling	Prevention of Mother to Child Transmission Program within the Antenatal Clinic	Yes
EA06	Voluntary Counseling and Testing (directly)	Voluntary Counseling and Testing (via Referral)	Yes
EA07	Inpatient Wards	Provider Initiated Testing and Counseling	No
EA08	Voluntary Counseling and Testing (directly)	Provider Initiated Testing and Counseling	Yes

Table 6 (Cont'd). Classification of the 29 Sites by Active Screening Entry Points based on Primary and Secondary Source of Patients.

Site (N=29)	Primary Source of Patients	Secondary Source of Patients	Site has Primarily Active Screening Entry Points
EA09	Voluntary Counseling and Testing (directly)	Prevention of Mother to Child Transmission Program within the Antenatal Clinic	Yes
EA10	Voluntary Counseling and Testing (directly)	Provider Initiated Testing and Counseling	Yes
EA11	Prevention of Mother to Child Transmission Program within the Antenatal Clinic	Voluntary Counseling and Testing (directly)	Yes
EA12	Voluntary Counseling and Testing (via Referral)	Provider Initiated Testing and Counseling	Yes
EA13	Voluntary Counseling and Testing (directly)	Voluntary Counseling and Testing (via Referral)	Yes
EA14	Voluntary Counseling and Testing (directly)	Tied between Provider Initiated Testing and Counseling and TB Clinic followed by Voluntary Counseling and Testing (directly)	Yes
EA15	Provider Initiated Testing and Counseling	TB Clinic	No

Table 6 (Cont'd). Classification of the 29 Sites by Active Screening Entry Points based on Primary and Secondary Source of Patients.

Site (N=29)	Primary Source of Patients	Secondary Source of Patients	Site has Primarily Active Screening Entry Points
EA16	Provider Initiated Testing and Counseling	Voluntary Counseling and Testing (directly)	Yes
EA17	Provider Initiated Testing and Counseling	Prevention of Mother to Child Transmission Program within the Antenatal Clinic	Yes
EA18	Inpatient Wards	Voluntary Counseling and Testing (directly)	No
EA19	Voluntary Counseling and Testing (directly)	Voluntary Counseling and Testing (via Referral)/ Other (Research)[tied]	Yes
EA20	Voluntary Counseling and Testing (directly)	Prevention of Mother to Child Transmission Program within the Antenatal Clinic	Yes
EA21	Voluntary Counseling and Testing (directly)	Prevention of Mother to Child Transmission Program within the Antenatal Clinic	Yes
EA22	Outpatient Ward	Inpatient Wards	No

Table 6 (Cont'd). Classification of the 29 Sites by Active Screening Entry Points based on Primary and Secondary Source of Patients

Site (N=29)	Primary Source of Patients	Secondary Source of Patients	Site has Primarily Active Screening Entry Points
EA23	Voluntary Counseling and Testing (directly)	Provider Initiated Testing and Counseling	Yes
EA27	Provider Initiated Testing and Counseling	Prevention of Mother to Child Transmission Program within the Antenatal Clinic	Yes
EA28	Voluntary Counseling and Testing (directly)	Prevention of Mother to Child Transmission Program within the Antenatal Clinic	Yes
EA30	Prevention of Mother to Child Transmission Program within the Antenatal Clinic	Voluntary Counseling and Testing (directly)	Yes
EA32	Voluntary Counseling and Testing (directly)	Outpatient Ward	No
EA33	Provider Initiated Testing and Counseling	Voluntary Counseling and Testing (directly)/Prevention of Mother to Child Transmission Program within the Antenatal Clinic[tied]	Yes

Table 6 (Cont'd). Classification of the 29 Sites by Active Screening Entry Points based on Primary and Secondary Source of Patients

Site (N=29)	Primary Source of Patients	Secondary Source of Patients	Site has Primarily Active Screening Entry Points
EA34	Prevention of Mother to Child Transmission Program within the Antenatal Clinic	Inpatient Wards	No

Figure 3A. Crude Mean CD4 Count at ART Initiation for Sites With Active Screening Entry Points.

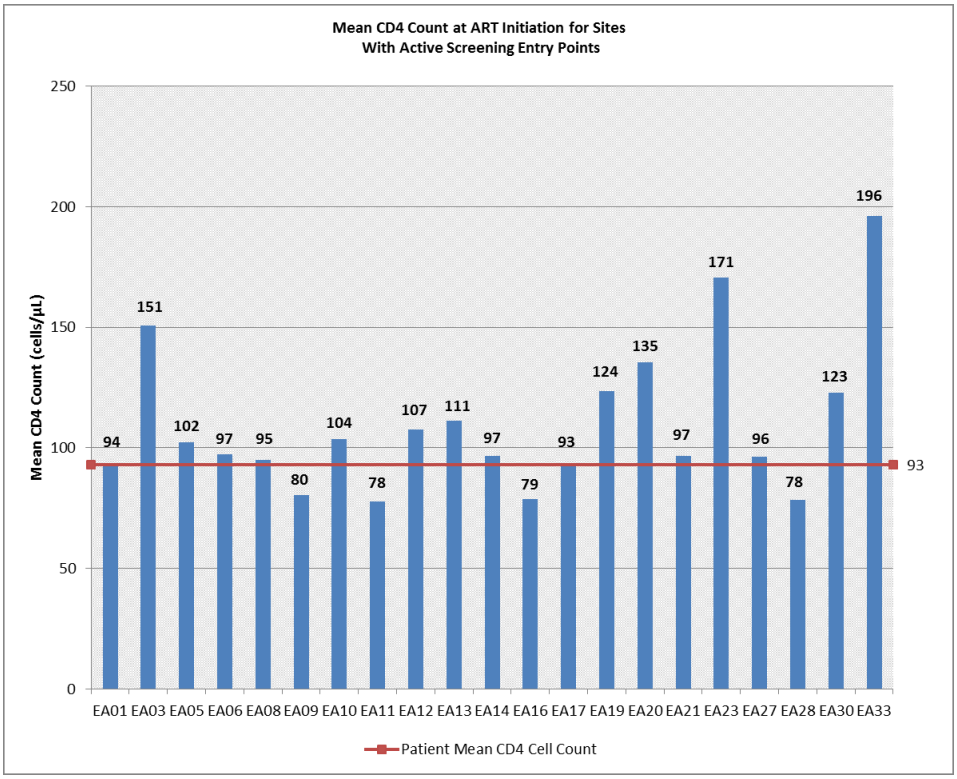


Figure 3B. Crude Mean CD4 Count at ART Initiation for Sites Without Active Screening Entry Points.

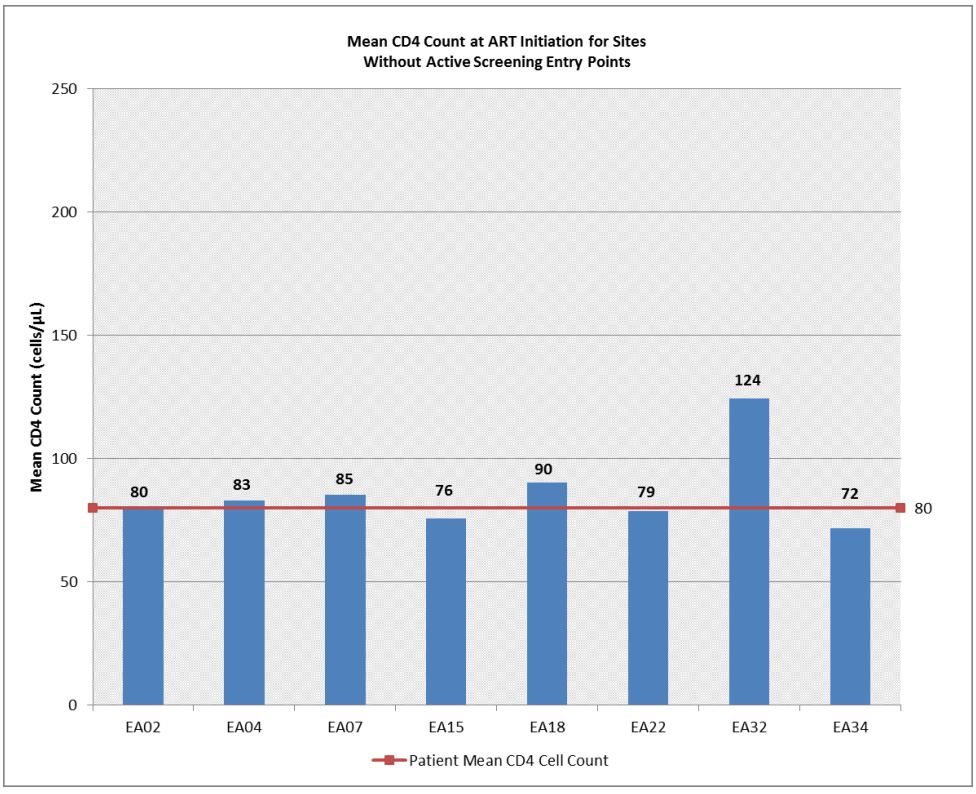


Table 7. Distribution of Potential Confounders and Associations with the Active Screening Entry Points (Exposure) and Patient CD4 Cell Count at ART Initiation (Outcome).

	Sites with Active Screening Entry Points	Sites without Active Screening Entry Points	Association with the Exposure	Association with the Outcome
	N (%)	N (%)	OR (P-value[1])	Mean CD4 Difference (P-value)
Patient-level Characteristics				
Number of Patients	24,725 (100)	20,616 (100)	--	--
Male Sex	8,348 (33.8)	7,845 (38.1)	0.84 (<0.09)	-22.3 (<0.0001)
Site and Programmatic-level Level Characteristics				
Number of Sites	21 (100)	8 (100)	--	--
Site Patient-Provider Ratio				
0.0 to 4.0	5 (23.8)	1 (12.5)	1.67 (1.00)	+33.3 (0.01)
4.01 to 8.5	5 (23.8)	3 (37.5)	0.56 (1.00)	+21.1 (0.04)
8.6 to 11.99	6 (28.6)	2 (25.0)	Reference	Reference
12.0 to 35.53	5 (23.8)	2 (25.0)	0.83 (1.00)	-1.7 (0.85)
Site's ART Eligibility Criterion for Patients in WHO Clinical Stage 1 or 2 (<200 vs 200+ cells/μL)	16 (76.2)	5 (62.5)	1.92 (0.65)	-23.0 (0.03)

[1]Fisher's Exact Test used due to expected cell values < 5.

Table 8. Mean CD4 Values for Crude and Adjusted Mixed Models Comparing Patients in Sites with and without Active Screening Entry Points.

Parameter	Model 1: Crude Mean CD4 (P-Value)	Model 2: Adj. for Patient Factors Mean CD4 (P-Value)	Model 3: Adj. for Programmatic Factors Mean CD4 (P-Value)	Model 4: Adj. for Patient and Programmatic Factors Mean CD4 (P-Value)
Active Screening Entry Points				
Yes	104.6 (0.03)	112.3 (0.04)	110.4 (0.004)	118.2 (0.005)
No	84.9 (ref)	92.7 (ref)	86.9 (ref)	94.5 (ref)
Sex				
Male	---	73.3 (<0.0001)	---	74.7 (<0.0001)
Female	---	92.7 (ref)	---	94.5 (ref)
Site Patient-Provider Ratio				
0-4.0	---	---	102.3 (0.23)	109.4 (0.26)
4.01-8.5	---	---	106.3 (0.03)	115.8 (0.03)
8.6-11.99	---	---	86.9 (ref)	94.5 (ref)
12-35.33	---	---	84.0 (0.70)	91.5 (0.71)
Site ART Eligibility Criteria for Patients in WHO Clinical Stage 1 or 2				
< 200 cells/μL	---	---	73.6 (0.11)	80.6 (0.12)
200+ cells/μL	---	---	86.9 (ref)	94.5 (ref)

Directed Acyclical Graphs

Active Screening – CD4 Cell Count at ART Initiation

Figure 4. Directed Acyclical Graph for Active Screening Model with Hypothesized Associations.

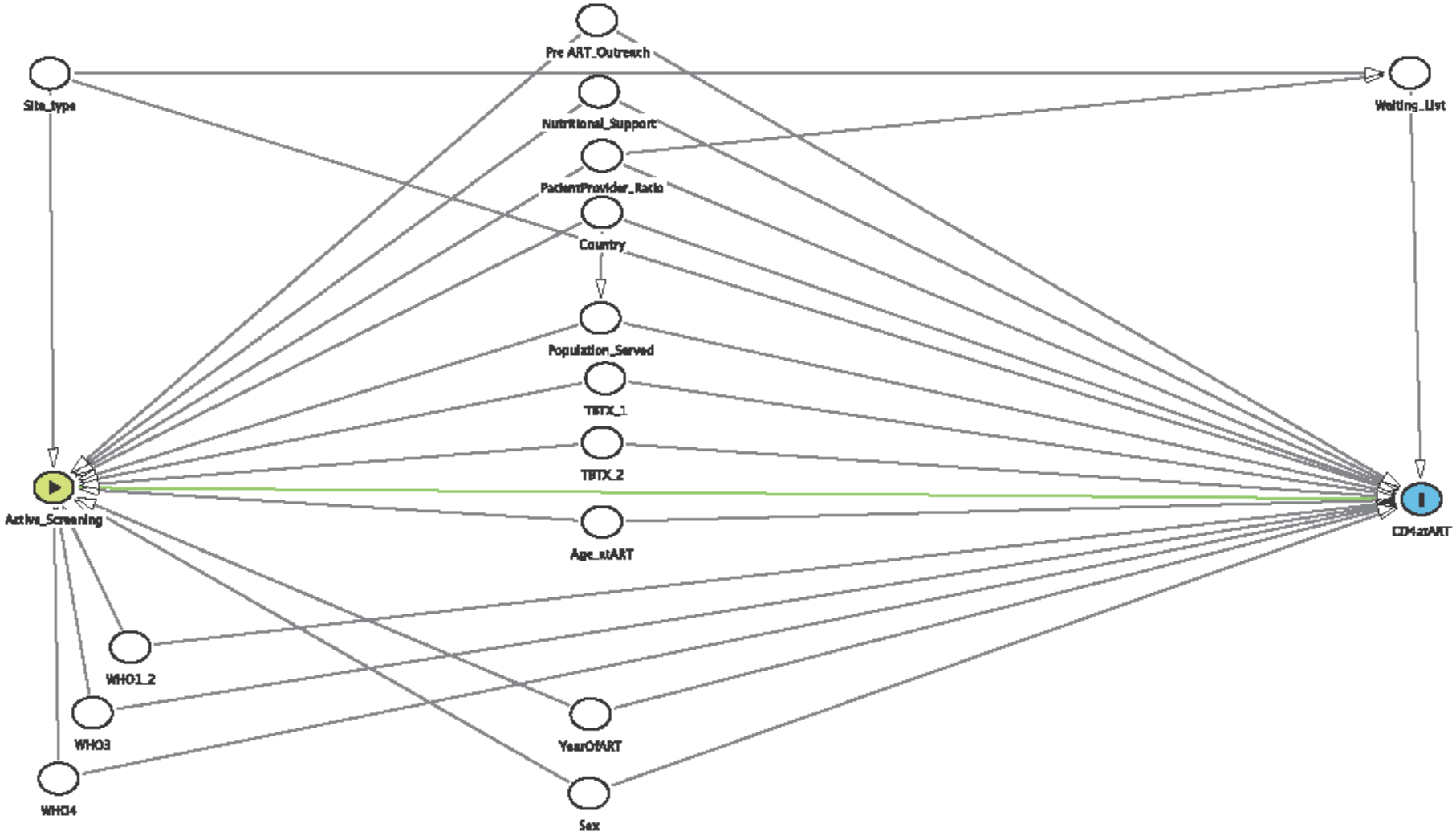


Figure 5. Directed Acyclical Graph for Active Screening Entry Points Model with Hypothesized Associations.

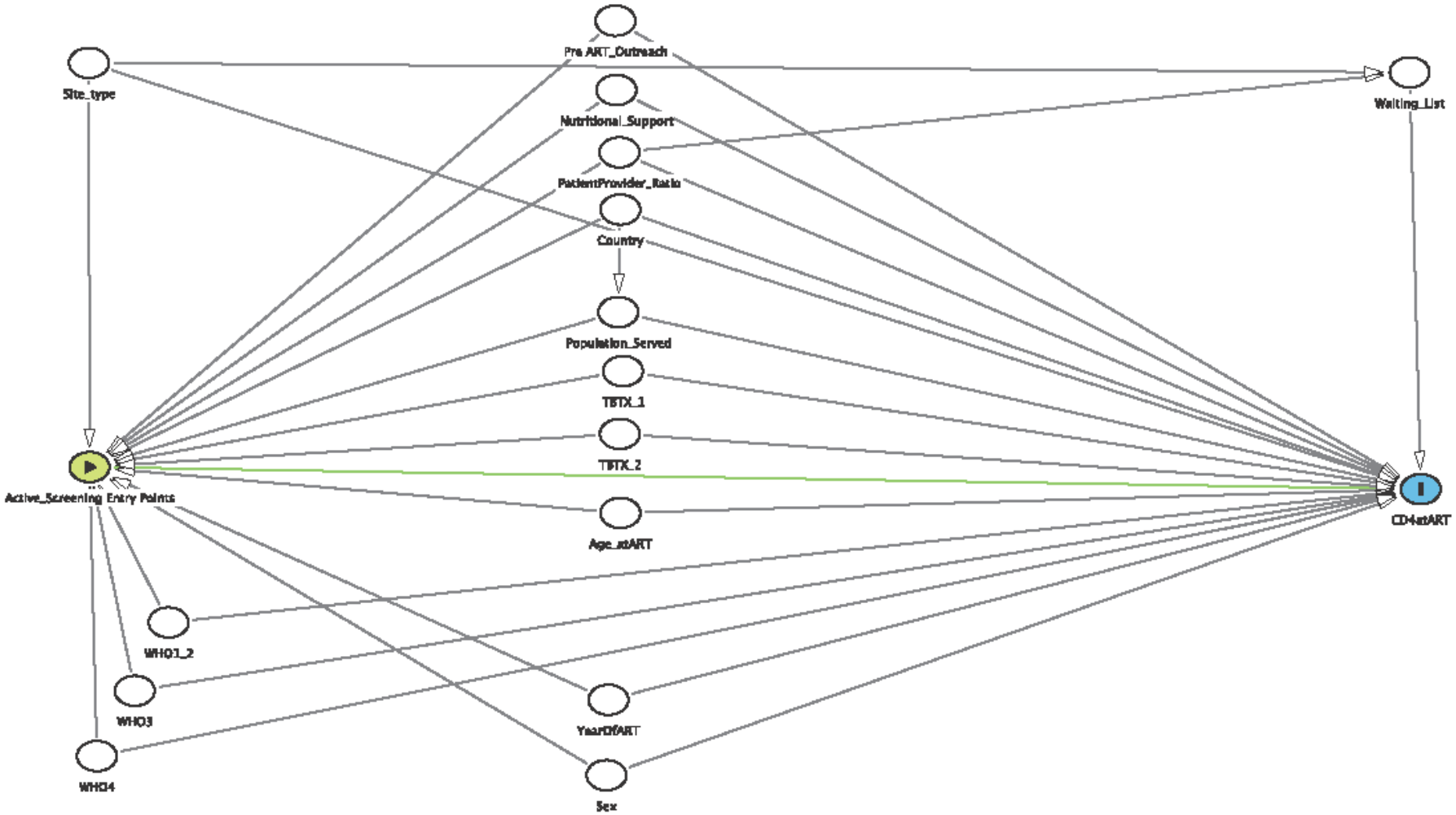


Figure 6. Directed Acyclical Graph for Active Screening Model Following Testing of Hypothesized Associations.

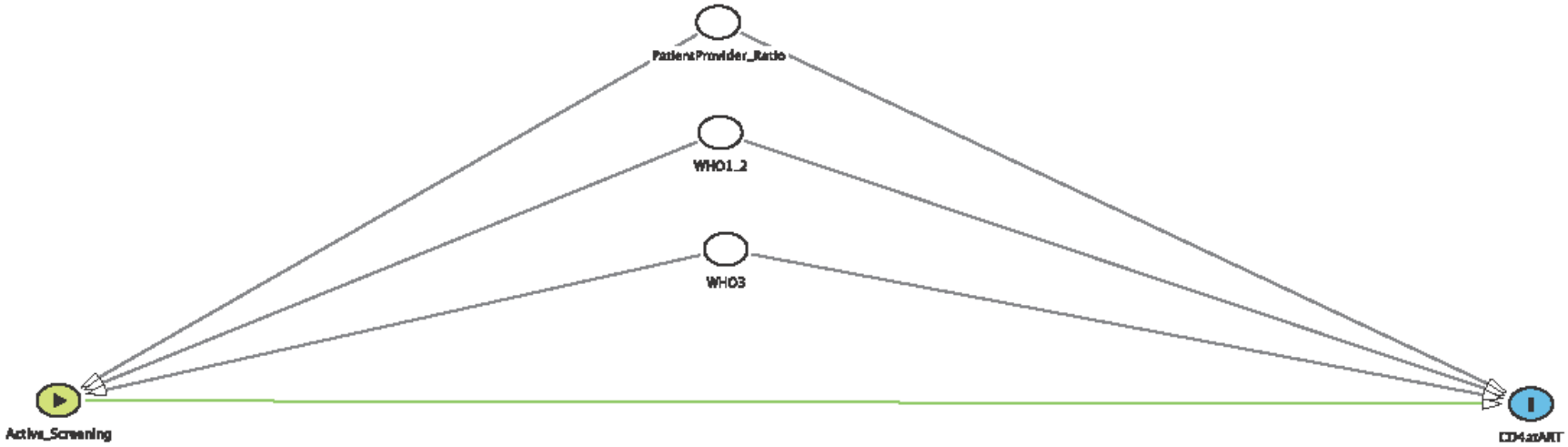
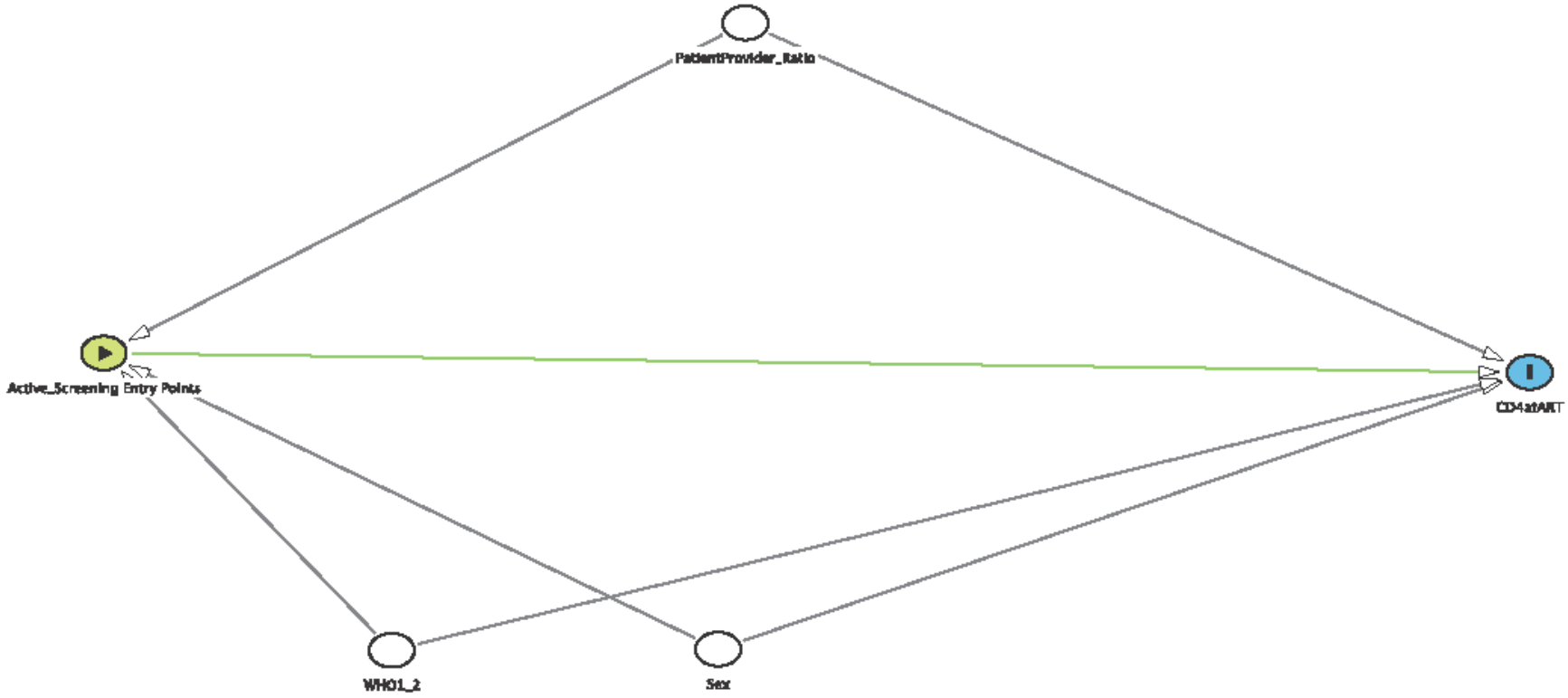


Figure 7. Directed Acyclical Graph for Active Screening Entry Points Model Following Testing of Hypothesized Associations.



Chapter 4. Does Active Screening for HIV Improve the Survival of Patients on Antiretroviral Therapy in sub-Saharan Africa?

Introduction

The positive trend in the scale-up of antiretroviral therapy (ART) in low- and middle-income countries has continued for over a decade. The number of HIV-patients receiving ART in these countries has increased from 300,000 in 2002 to 9.7 million by the end of 2012 [15, 33]. As a result, an estimated 4.2 million deaths have been prevented, life expectancy has increased for those on treatment, and HIV-transmission in the general population has been reduced [15, 32, 33]. Nonetheless, numerous challenges remain for those living with HIV in resource-limited countries. AIDS continues to be a significant contributor to premature mortality, and ART patients are more likely to die of AIDS than their counterparts in high-income countries.

In 2012 alone, 1.6 million people died of AIDS and over 90% of the deaths occurred in low- and middle-income countries [35]. Patients in low and middle-income countries are three-to-four times more likely to die during the first year of ART than those in high-income countries [5]. Lack of knowledge of HIV-status and late ART initiation, which may be a consequence of not being aware of one's status, are two major risk factors for AIDS-related mortality [1, 5, 12, 15, 40, 126-128]. Yet in sub-Saharan Africa, the region most heavily affected by the HIV-epidemic, half of those living with HIV are unaware of their status, and thus cannot benefit from the availability of ART [15, 33, 126]. In addition, the majority of the estimated 8 million HIV-patients in sub-Saharan Africa start ART late (i.e. during the advanced, symptomatic stages of the disease where CD4 cell counts tend to be low) when the risk of death is considerably higher [1, 8, 91, 92]. CD4 cell count is an indicator of HIV disease progression. Historically, the median CD4 count at ART initiation for patients in low- and middle-income countries has been below 200 cells/μL which is considered advanced by all of the World Health Organization ART guidelines issued during the past decade [1-3, 41, 43, 44, 92, 129, 130].

To help combat these challenges, the World Health Organization and other public health institutions have recommended the adoption of active screening (e.g. Provider-Initiated Testing and Counseling) with subsequent linkage to HIV prevention, care and treatment [14, 16, 17, 131]. Unlike Voluntary Counseling and Testing which is generally offered in stand-alone units and depends on a client's request for HIV testing, active screening is offered by the provider as part of standard care and thus is less hampered by testing and treatment barriers related to stigma, discrimination and lack of general knowledge of HIV/AIDS [131].

Active screening methods have been widely adopted since its recommendation seven years ago. Of 102 countries surveyed in 2012, 95% have drafted policies for Provider-Initiated Testing and Counseling [33]. Studies show that Provider-Initiated Testing and Counseling has high acceptability by clinicians and clients, and increases both the number of patients tested per provider and the rate of identification of HIV-positive individuals [13, 49-51]. It has also been applied successfully in antenatal clinics as a means to 1) prevent mother to child transmission of HIV, and 2) enroll women on ART earlier than they would otherwise [33, 103, 132]. In previous analyses, I showed that patients in HIV/AIDS care and treatment sites receiving patients primarily from active screening HIV-related services (e.g. antenatal clinics with Provider-Initiated Testing and Counseling for the prevention of mother to child transmission of HIV) start ART with modestly higher CD4 cell counts than those in sites receiving patients primarily from non-active screening entry points (e.g. Tuberculosis Treatment Programs, Inpatient Wards). However, whether these higher CD4 cell counts at ART initiation translate into improved survival merits further investigation, and such is the primary goal of this study.

I used programmatic, contextual and routinely-collected patient data from HIV care and treatment sites in sub-Saharan Africa to investigate whether implementation of active screening programs in the context of resource-limited settings lead to improved patient survival. I hypothesize that HIV/AIDS care and treatment sites receiving patients primarily from active screening entry points (e.g. antenatal clinics with Prevention of Mother to Child Transmission program) have better patient survival than sites whose patients come primarily from non-active screening entry points (e.g. Tuberculosis Treatment Programs, Inpatient Wards). Secondly, I hypothesize that this association is mediated, at least in part, by the patient's CD4 cell count at ART initiation.

Methods

Data Source

Data for this analysis come from the International Epidemiologic Databases to Evaluate AIDS (IeDEA) (http://www.iedea-ea.org). The IeDEA initiative is a worldwide research collaboration established in 2005 to identify optimal treatment and prevention strategies across diverse economic, geographical, and cultural settings. The consortium is composed of health sites and research institutions in several countries and regions: Asia/Pacific, the Caribbean, Central and South America, Canada, the United States, West Africa, Central Africa, East Africa and Southern Africa [106]. East Africa is the region providing the data for this analysis.

A site is composed of one or more clinics. To participate in the initiative, sites must 1) provide ART to HIV/AIDS patients, 2) follow patients prospectively, 3) collect data electronically, and 4) adhere to a standardized protocol for data collection. Patients aged 18 year or older at the time of ART initiation, who commenced ART between the years 2003 and 2008 were eligible for this study. Prior to analysis, the data were submitted electronically to the regional data center at Indiana University for merging and validation. Collection of these data was approved by both Indiana University's and Columbia University's Institutional Review Boards (IRBs) as well as country (Uganda's National Council on Science and Technology, Tanzania's National Institute for Medical Research) and local (Moi University's Institutional Research and Ethics Committee, Kenya Medical Research Institute, Mbarara IRB) IRBs.

Twenty-nine HIV/AIDS care and treatment sites provided routinely collected data on 45,359 patients who started ART during 2003-2008. Thirteen (0.03%) patients who had CD4 results outside the plausible range (i.e. > 1,600 cells/μL), and five (0.01%) patients whose last visit date was recorded as occurring before ART initiation were excluded. The analytical sample size was 45,341 patients from twenty-nine sites.

Patient-Level Data

Patient information was routinely collected by the site's staff where HIV/AIDS care and treatment was provided. The staff followed a standard IeDEA-prescribed protocol thus the data were standardized across sites prior to submitting to Indiana University's regional data center. Data included demographic (e.g. sex, date of birth, socio-economic status), clinical (e.g. WHO clinical stage, presence of tuberculosis disease and Kaposi's sarcoma at ART initiation), laboratory (e.g. CD4 cell count at ART initiation, presence of anemia at enrollment), and treatment status (e.g. lost to follow-up, dead, date of death) information.

Site and Program-Level Data

Information on site characteristics and programmatic activities, including those associated with a site's primary entry points, was collected using the IeDEA Site Assessment Tool (see Appendix B). The assessment tool was used to collect information on the site's physical characteristics, programmatic activities and population served. This included attributes such as 1) type of site (e.g. health center/clinic, district/provincial hospital or teaching/national referral hospital), 2) policies followed (e.g. CD4 and World Health Organization stage criteria to start ART, charging of fees for laboratory, medication and other services), 3) resources available (e.g. number of patient beds, number and types of providers and availability, tuberculosis diagnosis and treatment), and 4) patient support services provided (e.g. adherence support, types of emotional, nutritional and pre-natal services) at the site. Additional information on the population served (e.g. urban, rural, semi-urban residents) and the primary entry points (e.g. antenatal clinics, voluntary counseling and testing units, tuberculosis clinics) referring patients to the site was also collected with this tool.

Measures

Outcome variable

The main outcome was death. Patient survival time was calculated in months and by taking the difference between the date of ART initiation and the date of death. For patients known to have died but who lacked a recorded date of death, the last recorded site visit date was used as a surrogate date of death. Patients who did not die were followed until their last visit, discontinued ART at the site, or up to closure of the database (in 2008 or 2009 depending on the site or HIV/AIDS program). A patient was defined as being lost to follow-up if he or she did not have a clinic visit within three months of database closure without documented evidence of death or transfer to another site. See "Outcome variable", Appendix A for more details on patients lost to follow-up.

Exposure variable

The main exposure of interest was whether the site's primary sources of patient referral were entry points likely to conduct active screening. I utilized information provided in the IeDEA Site Assessment Tool (see Question A15 on p.183, Appendix B) to classify sites as having mainly "Active Screening Entry Points" or "non-Active Screening Entry Points." The classification was based on the site's primary and secondary referral sources of patients. Entry Points where active screening was expected to be conducted included: Provider Initiated Testing and Counseling, Prevention of Mother to Child Transmission, and Other (Research); entry points where active screening was not expected to be conducted included: Tuberculosis Clinics, In-patient Wards, and Outpatient Wards. Voluntary Counseling and Testing units were treated as entry points where both active screening and diagnostic testing (not a form of active screening) may be conducted since these test both subjects referred for routine testing or due to the

appearance of symptoms. A site was classified as having "Active Screening Entry Points" if 1) both the primary and secondary entry points included those expected to conduct active screening, 2) one of the active screening entry points was paired with Voluntary Counseling and Testing, or 3) both the primary and secondary entry points were Voluntary Counseling and Testing units. Sites with Tuberculosis Clinic, Inpatient or Outpatient Ward as one of its entry points were classified as having "non-Active Screening Entry Points." In five instances, two distinct entry points were ranked equally for either the most (1/5) or second most (4/5) common referral source of patients. In all but one instance, the equal ranking did not influence the classification of the site since the entry points were concordant with regard to active screening. In the instance it did (site "EA14"), the third most common referral source of patients was used to determine the classification of the site.

Mediator Variable

A patient's CD4 cell count at the time of ART initiation, a measure of disease progression, was assessed as a potential mediator of the relationship between "Active Screening Entry Points and death. The CD4 cell count measured closest to the date of ART initiation was used. CD4 measurements taken no more than six months prior to or no more than fourteen days after the start of ART were considered (CD4 cell counts was analyzed as a log-transformed continuous variable in regression models; CD4 values equal to 0 were changed to 1 prior to transformation).

Potential Confounders

Patient, programmatic and site level variables hypothesized to be common causes of the exposure, outcome and mediator variable were considered for statistical adjustment. The identification of these variables was based on a review of the HIV/AIDS literature and subject-matter knowledge.

Patient-level Variables

Patient-level variables included sex (reference group: females), age at ART initiation (reference group: ages 30-35), and year of ART initiation (reference group: 2008) [5, 80, 92, 99]. See "Potential Confounders", Appendix A for more information on these variables and other patient-level variables considered but excluded.

Programmatic-level Variables

Programmatic-level variables included presence of 1) nutritional support for all patients (reference group: absence), 2) outreach program for non-ART patients who missed visits (reference group: absence), 3) ART waiting list for eligible patients (reference group: absence), 4) tuberculosis clinic on-site (reference group: sites referring patients off-site for tuberculosis treatment), and 5) tuberculosis treatment onsite but without an onsite tuberculosis clinic (reference group: sites referring patients off-site for tuberculosis treatment) [5, 107-109]. The site's ART eligibility criteria for each World Health Organization clinical stage were also considered [110].

The ART eligibility criteria were based on the required CD4 cell count to initiate ART per World Health Organization (WHO) clinical stage (criteria for WHO stages I and II (combined), III, and IV). The CD4 thresholds used for each clinical stage were based on the cut-points reported by sites per stage, and the WHO ART guidelines in effect during the study's

follow-up period. See Potential Confounders, Appendix A for more details on this construct, and other programmatic-level variables considered but excluded.

Contextual-level Variables

Contextual variables included 1) country location (Kenya (reference group), Uganda, or Tanzania), 2) site type (health center/clinic, district/provincial hospital (reference group), or teaching/national referral hospital, 3) patient population served (mainly urban, mainly rural (reference group), and in between urban and rural), and 4) Patient-provider ratio [29, 83, 95, 111-114]. Note that due to a small number of sites located in Tanzania, country location was excluded from regression analyses but investigated as a potential confounding factor (see Sensitivity Analysis below for more how this issue was addressed). Patient-provider ratio was divided into four categories (ratios 0-4.0, 4.01-8.5, 8.6-11.99 (reference group), and 12-35.53). See Potential Confounders, Appendix A for more details on how patient-provider ratio was calculated and other contextual variables considered but excluded.

Statistical Analysis

Data Validation and Descriptive Analysis

Standard data validation was conducted to identify potential missing and implausible values and assess the distribution of continuous variables. Descriptive statistics of key patient and contextual measures were calculated. Median values and ranges are reported as measures of central tendency for continuous variables not normally distributed, while frequencies and proportions are reported for categorical variables.

Selection of Potential Confounders

Selection of potential confounders was completed in three steps. First, based on a review of the literature and subject-matter knowledge Directed Acyclical Graphs (DAG) hypothesizing the relationships among the main exposure, outcome, mediator and potential confounders were drawn (See Figure 3). Second, the strength and statistical significance of each bivariable association was measured (to account for clustering of patients within sites, simple linear and logistic regression with random intercepts or Cox Proportional models with robust sandwich estimator of variance were used when needed) [115-118]. Lastly, variables associated (OR or HR $\geq$ 1.20 and/or P-value $\leq$ 0.10, in this instance) with at least two other variables were considered for statistical adjustment. The following variables were considered as potential confounders of the exposure-disease relationship: 1) Site type, 2) Site's patient-provider ratio, 3) Presence of an ART waiting list for eligible patients, 4) Patient population served by site, 5) Site's ART eligibility criterion for WHO clinical stage I/II, 6) Site's country location, and 7) Sex; the following were considered as potential confounders of mediator-disease relationship: 1) Site type, 2) Site's patient-provider ratio, 3) Age at ART initiation, and 4) Sex (See Figure 4).

Multivariable Analysis

First, I stratified the data by "Active Screening Entry Points" to calculate crude median survival time and incidence rate, and generate crude Kaplan-Meier survival curves. Marginal Cox Proportional models (with robust sandwich estimators of variance to account for clustering) were then fitted (See "Assessment of the Statistical Assumptions for Cox Proportional Hazards Models", Appendix A for more information). The multivariable analysis began with a bivariable model to estimate the crude association between the main exposure and outcome variable. Four additional multivariable models adjusting for potential confounders were then fitted. DAG

techniques as described by Greenland, Pearl, and Robins were employed to select the minimal set of potential confounders needed for adjustment [119]. Potential confounders which improved the precision of confidence intervals but which were not selected for the minimal set were also considered for adjustment.

The first adjusted model included the main exposure variable with level-1 covariate only (Sex); the second adjusted model included the main exposure variable with level-2 covariates only (Site type, Site's patient-provider ratio, Presence of a waiting list at site, Patient population served by site, Site's ART eligibility criterion for WHO clinical stage I/II); and the third and fourth adjusted models included the main exposure with level-1 and leve-2 covariates (with and without the variable presence of a waiting list at the site). To assess for evidence of confounding the betas estimated for the main exposure in the crude and the final model were compared. Presence of confounding was defined as a change of 10% or more in the main exposure beta. Lastly, adjusted survival curves based on the final model were generated comparing patients in active and non-active screening entry point sites. The value used for each confounder was its corresponding mean.

Assessment of Mediation

We first measured the association between the main exposure and the mediator, and then between the mediator and the outcome [133]. Once these relationships were established, we assessed for effect measure modification of the main exposure and potential mediator. This was performed by 1) stratifying on the levels of the main exposure and comparing the association between the potential mediator and the outcome by each stratified level, and 2) considering the size of the parameter and degree of statistical significance for an interaction term of the main exposure and potential mediator. Since evidence of effect measure modification was not

sufficiently present to necessitate considering alternative tests of mediation (e.g. Sobel test), mediation was tested by fitting the final model plus the variable "Age at ART initiation" (the only potential confounder of the mediator-outcome relationship not included in the final model) with and without the potential mediator in an extended Cox model to meet the proportional hazards assumption. Evidence of mediation was supported by a change of 10% or more in the direction of the null value for the main exposure beta once the mediator was added to the model [133].

Sensitivity Analysis

Additional analyses were conducted to assess the influence on study conclusions of 1) unadjusted potential confounders, 2) evidence of potential violation of the proportional hazards assumption, 3) outlier values of CD4 at ART initiation, and 4) lost to follow-up. Due to the small number of sites in Tanzania (n=2) and Uganda (n=4) and proportion of missing values, the final model was not adjusted for site's country location or measures of socio-economic status. To assess if study results were confounded due to exclusion of country location, I re-fitted the final model limiting it to sites in Kenya which accounted for 79% and 74% of sites and patients, respectively. To assess the potential influence of patient socio-economic status, which was not adjusted due to large number of missing values, appropriate measures of socioeconomic status for East Africa (e.g. level of education, availability of electricity and piped water in the home) were added to the hypothesized DAGs. I then assessed the need to adjust for these measures socio-economic status by determining the minimal set of variables needed to address confounding.

During assessment of the proportional hazards assumption, the results hinted to potential violation of the assumption by the variables patient-provider ratio and site type. Although upon re-assessment of the proportional hazards assumption adjusting for other variables in the model no evidence of violation was detected, I re-fitted the final model using extended and stratified Cox models assuming violation of the assumption by these variables was present. The results and conclusions drawn from the refitted models were compared with those from the standard Cox Proportional model. The Akaike Information Criterion (AIC) and evidence of improved precision in estimating the parameter for the main exposure were also considered during this comparison.

To account for the potential influence of outliers, the mediation analysis was repeated operationalizing CD4 cell count at ART initiation using quartiles (reference group: log CD4 < 3.95 (or 51 cells/μL)), and the clinically significant cut-point of 200 cells/μL (using the log CD4 value: 5.30 cells/μL). The cut-point of 350 cells/μL could not be tested due to small number of subjects with CD4 cell counts at ART initiation above this point.

The potential introduction of bias due to early attrition was assessed through a subset analysis focused on patients who were lost to follow-up or died within the first year of ART initiation. The proportion of patients lost to follow-up or recorded as dead within 12 months of ART initiation were compared between sites with active and non-active screening entry point. The last recorded CD4 cell count and the CD4 cell count at initiation for those lost to follow-up in the first year of ART were also compared between these sites to assess for mean differences. Lastly the final model was refitted assuming that among patients lost to follow-up within the first year of ART initiation, those from Active Screening Entry Point sites survived and those from non-Active Screening Entry Point sites died. All analyses were performed in SAS® Version 9.2.

Results

Patient and Contextual Characteristics of Study Population

Table 1 shows that most of the 45,341 patients initiated ART in Kenya, which accounted for 33,586 (74%) patients in 23 (79%) sites, followed by Uganda with 9,737 (21%) patients in 4 (14%) sites, and Tanzania with 2,018 (4%) patients in 2 (7%) sites. Patients predominantly received care in teaching/national referral hospitals (40.9%) and district/provincial hospitals (38.0%). The percentage of patients initiated on ART increased each year until 2008 with the largest increases in earlier years. The median age at the start of ART was 37 years (range: 18 to 88 years), and 64.3% were female. The median survival time was 14.2 months (range: 0 to 75.6 months), and the total person-time of follow-up was 809,860 months. A total of 3,082 (6.8%) deaths were documented in the study population, and 13,253 (29.2%) patients were lost to follow-up.

As shown in Table 2, the total number of patients initiated on treatment during the six-year period ranged from 55 to 8,592 per site among the twenty-nine sites. The variation was partly due to differences in the number of years sites have been providing ART. The patient median age per site ranged from 21 to 40 years, and at each site more than half of the patients were women (range: 58.7-100%).

Table 3 lists the primary and secondary source of patients and classification of active screening by site. Of the twenty-nine sites, twenty-two (75.9%) were classified as having primarily "Active Screening Entry Points" and seven (24.1%) were classified as having primarily "non-Active Screening Entry Points." Among "Active Screening Entry Points" sites, the most common primary or secondary entry point was Voluntary Counseling and Testing unit (24/44 or 54.5%) followed by Provider Initiated Testing and Counseling (11/44 or 25.0%) and Prevention

of Mother to Child Transmission (9/44 or 20.5%). Among "non-Active Screening Entry Points" sites, the most common entry point was In-patient Ward (5/14 or 35.7%) followed by Provider Initiated Testing and Counseling (3/14 or 21.4%), and a tie between Outpatient Ward and Voluntary Counseling and Testing (2/14 sites or 14.3% for each).

Association between Active Screening and Patient Survival

Figure 1 compares the crude survival probability of patients in active screening and non-active screening entry point sites. Patients in sites with primarily Active Screening Entry Points show worse survival than those in sites with primarily non-Active Screening Entry Points. The patient and contextual variables selected for statistical adjustment and their respective association with the exposure and outcome are listed in Table 4. Active screening sites had a lower percentage of male patients, of teaching/national hospitals and sites with a patient-provider ratio in the range of 4.01-8.5. These sites were also less likely to serve predominantly non-urban patients and more likely to initiate patients with WHO clinical stage I or II only after reaching a CD4 cell count below 200 cells/μL. Patients receiving ART in teaching/national hospitals and in sites with the lowest patient-provider ratio (0.0-4.0) were associated with lower rates of mortality. Male patients and patients receiving treatment in sites serving predominantly non-urban patients or sites requiring a CD4 cell below 200 cells/μL for ART initiation had higher rates of mortality.

Table 5 presents the five Cox models fitted. In accordance with the crude Kaplan Meier curves, patients in Active Screening Entry Point sites had a rate of death 1.32 (95% CI: 1.03-1.70) times higher than those in non-Active Screening Entry Point sites. Adjusting for sex (Model 2) did not materially change the results. However, following adjustment for programmatic and contextual factors (Site type, Site's patient-provider ratio, Presence of a

waiting list at site, Patient population served by site, Site's ART eligibility criterion for WHO clinical stage I/II) in Model 3, the mortality rate for patients in Active Screening sites decreased (HR: 0.83; 95% CI: 0.65-1.07) below that of patients in non-Active Screening Entry Point sites. The change is mainly attributed to the factors "Site type" and "Patient population served" (the addition of these two variables alone to the patient factor adjusted model results in a HR (95% CI) of 0.85 (0.66-1.09). As described in the previous paragraph, patients who receive treatment in teaching/national hospitals and sites serving predominantly urban patients showed better survival and were unevenly distributed between Active and non-Active Screening Entry Point sites. Among Active Screening Entry Point sites, patients from teaching/national hospitals only accounted for 3.8% of the population but for 85% of the non-Active Screening Entry Point population. Similarly, patients in sites serving predominantly urban patients accounted for 57.7% of the Active Screening Entry Point population but for 80% of the non-Active Screening Entry Point population. Thus, the distribution of patients with better survival favored non-Active Screening Entry Point sites but after adjustment this source of confounding was addressed.

Models 4 (HR: 0.83; 95% CI: 0.63-1.09) and 5 (HR: 0.82; 95% CI: 0.64-1.06) adjust for patient, programmatic and contextual-level factors and show virtually no change in the estimates with one exception. Model 5, the final model, shows that adjusting for presence of a waiting list at the site, which is not included in the minimal set of variables needed for adjustment, leads to approximately a 9% improvement in the precision of the 95% confidence intervals (width decreases 8.7% from 0.46 to 0.42 points). Despite the improved precision, the results of the final and nearly all other adjusted models narrowly miss statistical significance. Lastly, Figure 2 displays survival curves for active screening and non-active screening sites based on the final

model (Model 5). The figure displays the better survival probability for patients in sites with predominantly Active Screening Entry Points.

Assessment of CD4 Cell Count at ART as a Mediator of the Association Between Active Screening Entry Point and Patient Survival

The results presented in Table 6 establish that there are significant associations between Active Screening Entry Point and CD4 cell count at ART initiation, and CD4 cell count at ART initiation and patient survival. The results of the stratified analysis (Table 6) and those of a test for multiplicative interaction (not shown; p-value 0.58) suggest that the association between the proposed mediator and the outcome do not vary appreciably by levels of the main exposure. As shown in Table 7 adding the mediator patient CD4 cell count at ART initiation and age at ART initiation, a potential confounder of the mediator-outcome association, to the final model led to a decrease towards the null of 64.7% [-0.19493-(-0.06864)/-0.19493] for the beta estimate of the main exposure. The change translated to an increase in the Hazard Ratio towards the null value from 0.82 to 0.93.

Sensitivity Analyses

Adjusting for country location by limiting the data to sites in Kenya, and fitting separate stratified Cox models assuming presence of violation in the Proportional Hazards Assumption by patient-provider ratio and site type did not lead to improvements in the models or changes in study conclusions (See Table 8, "Results – Sensitivity Analyses", Appendix A for more information).

I hypothesized that patient socioeconomic status would be associated independently with the main exposure and outcome directly and via potential confounders site type, site patient-provider ratio, sex, and patient's degree of adherence to ART. With the exception of ART adherence, all of these factors were accounted in the final model and doing so restricted the

influence of patient socioeconomic status on the study findings given the hypothesized relationships among these variables. However, patient ART adherence, which is known to be associated with survival, was unmeasured and could not be adjusted indirectly through other variables. If sites with non-Active Screening Entry Points have a considerably higher proportion of patients with lower socioeconomic status and these patients indeed have worse survival, not adjusting for this factor may lead to a protective hazard ratio as observed in our results.

The test for mediation using a stratified model with CD4 cell count at ART initiation operationalized as quartiles, to account for the potential influence of outliers, did not change study conclusions regarding mediation. However, when the mediation variable was dichotomized at 200 cells/μL, the results did not support evidence of mediation (See Table 9, "Results – Sensitivity Analyses", Appendix A for more information).

Within one year of ART initiation, 8,680 patients were lost to follow-up and 2,469 were recorded as dead. The proportion lost to follow-up (19.2% vs. 19.0%; OR: 0.99 (0.7-1.5)) or recorded as dead (6.0% vs. 4.8%; OR: 1.03 (0.6-1.8)) did not differ materially between active and non-active screening sites (See Table 10, "Results – Sensitivity Analyses", Appendix A for more information). The mean CD4 cell count last recorded (112.8 cells/μL vs. 92.0 cells/μL, p-value: 0.045) and at ART initiation (84.0 cells/μL vs. 73.2 cells/μL, p-value: 0.06) were higher for patients in sites with primarily active screening entry points (See Table 11, "Results – Sensitivity Analyses", Appendix A for more information). The median difference in months between the date of last recorded CD4 and last scheduled visit was similar for patients in sites with mainly active and non-active screening entry points (2.4 months vs. 2.6 months). Lastly, assuming that patients lost to follow-up within the first year from Active Screening Entry Point sites survived while those from non-Active Screening Entry Point sites died led to a hazard ratio

of 0.27 (95% CI: 0.24-0.29) when the final model was refitted. Conversely, assuming that the former died while the latter patients survived led to a hazard ratio of 3.25 (95% CI: 2.28-4.63) (See Tables 12 and 13, “Results – Sensitivity Analyses”, Appendix A for details)

Discussion

The results show that the rate of death for patients in sites with primarily active screening entry points (e.g. Provider Initiated Testing and Counseling, Prevention of Mother-to-Child Transmission) is not statistically different than that of patients in sites with primarily non-active screening entry points (e.g. In or Outpatient Wards, Tuberculosis clinics). Several factors including lack of adherence to ART, programmatic-related delays in ART initiation, and/or low CD4 cell count at ART initiation may explain the findings. ART adherence is the most important predictor of survival once treatment is initiated [127]. Any survival advantage gained by an earlier diagnosis would be diminished by poor adherence. Though not measured in our study, the existing literature shows respectable levels of adherence for patients in these settings [134]. In addition, the Cox models were adjusted for site patient-provider ratio and site type which can influence ART adherence indirectly. Lastly, all of the sites offered ART adherence support at and after ART initiation. Thus, even though we cannot rule out adherence as a factor, we have no evidence to suspect there was a significant difference in ART adherence between the comparison groups.

Programmatic-delays in ART initiation can diminish any survival advantage gained from an earlier diagnosis due to active screening. Though patients in sites with active screening entry point started ART generally 13 days earlier than those in sites with non-active screening entry points, this difference was not statistically significant and adjusting for it did not materially change study results. The most likely factor explaining our findings is the low patient CD4 cell count at ART initiation. CD4 cell count at ART initiation is a well-established predictor of survival [5, 8, 127]. The mean CD4 cell count at ART initiation for patients in sites with active screening entry points, 118.2 cells/μL, is well-below the current (500 cells/μL) and former (200

cells/μL) World Health Organization's threshold for ART initiation [41, 43, 44]. Thus, even in the best case scenario patients in our study population typically started ART at advanced stages of the infection and as a result were at an increased risk of death.

It is worth noting that despite the challenging circumstances under which active screening was implemented, the results are in the expected direction [HR (95% CI): 0.82 (0.64 – 1.06)]. HIV-positive individuals in resource-limited settings face multiple challenges which hinder HIV testing (provider or patient-initiated) and linkage to the treatment cascade resulting in increased risk of death [1, 65, 97, 100, 135]. In addition, most healthcare systems in low- and middle-income countries are in a weak state and are poorly integrated. These conditions limit the opportunities for provider to interact with patients and prescribe an HIV test before the infection has progressed to AIDS. In those instances where people living with HIV have been diagnosed early in the infection, structural barriers may impede timely ART initiation thus hampering the potential benefits of active screening on survival [14, 91].

To our knowledge this is the first study testing the association between active screening at the clinic level and survival. Most studies on active screening have focused primarily on the acceptability of provider-initiated testing, and the rate of identification of previously undiagnosed people living with HIV [11, 50, 136]. Thus, we cannot compare our main findings. However, similar to other studies the mean patient CD4 cell count at ART initiation was low independent of potential exposure to active screening [49, 99, 120].

There are some study limitations. The classification of entry points as active or non-active screening was based on how HIV related services operated historically and not on survey data. Nonetheless, for entry points such as Provider Initiated Testing and Counseling and Prevention of Mother-to-Child Transmission active screening has always been a defining

characteristic of these programs while for others, such as TB clinics, it was not the norm at the time of this study and therefore misclassification in an unlikely contributing factor. Four of the seven NASEP sites included an active screening entry point (three had Provider Initiated Testing and Counseling, and one had Prevention of Mother-to-Child Transmission) paired with a non-active screening entry point. This likely contributed to underestimation of the protective effect of active screening since it made non-Active Screening Entry Point sites more similar to Active Screening Entry Point sites. The programmatic and site level data collected through the IeDEA Site Assessment Tool reflects information at one point in time which may not reflect conditions present during the entire follow-up period, thus potentially limiting our ability to fully adjust for potential confounders.

A considerable amount of the study patient population was lost to follow-up. Studies have shown that ART patients lost to follow-up, especially shortly after ART initiation, have higher probabilities of death which result in an overestimation of survival rates [137-140]. The sensitivity analysis showed no statistically significant difference in the proportion of patients lost to follow-up or recorded as dead within one year of ART initiation between active and non-active screening sites. Therefore, it is unlikely that patient attrition biased study results. However, if a bias was introduced due to attrition it may bias the study results towards the null since patients lost to follow-up from active screening sites had higher mean CD4 cell count at ART initiation (+11 cells/μL) and at last follow-up (+21 cells/μL). As shown in our analysis, if we were to assume that all patients lost to follow-up from Active Screening Entry-Point sites survived while all those from non-Active Screening Entry Point sites died (or vice-versa), the results, (HR: 0.27; 95% CI: 0.24-0.29; or vice versa HR: 3.25; 95% CI: 2.28-4.63) would be sufficient to change our study conclusions. Despite the findings of the sensitivity analysis, it is

unknown whether attrition can bias our findings since studies in this area have not investigated its impact on programmatic level factors [137, 139, 140]. We will further investigate this issue in future analyses.

This study has several strengths. To our knowledge, this is the first study investigating the relationship between active screening at the clinic level and survival. The dataset has a substantial number of sites each with a considerable number of ART patients. The sites were from diverse geographic settings and data collection extended over several years. The completeness of the data was high for all the variables included in the final model. The multi-level models were adjusted for individual, programmatic and contextual variables which is uncommon in these types of studies. Finally, given the nature of the data collection the results represent real world conditions and thus account for barriers to HIV testing and ART initiation operating in these settings. The results are likely generalizable to resource-limited settings with sub-optimal health-care systems and a generalized HIV epidemic.

Conclusions

AIDS remains one of the main causes of premature mortality in low- and middle-income countries mainly because of lack of knowledge of HIV status and late ART initiation [1, 12, 15, 35]. Active screening for HIV has been promoted and adopted as a strategy to identify and treat HIV-positive individuals during the early stages of the infection [16, 131]. Our findings failed to demonstrate a statistically significant advantage in survival for patients is sites with primarily active screening entry points. The association, however, is in the expected direction. Independent of these findings, the demonstrated benefits of active screening (e.g. high acceptability, increased number of patients tested and higher rate of identification of previously undiagnosed people living with HIV) support adoption of this intervention particularly in regions with a high HIV burden and where a low proportion of the population is unaware of their HIV status. To become effective in improving survival, the implementation of active screening programs in low- and middle-income countries may require a systematic shift to a more preventative approach to healthcare and improved referral mechanism to efficiently bring those in need into treatment. This will increase the opportunities for practitioners to identify HIV-positive individuals earlier in the infection.

Tables and Figures

Active Screening Entry Points – Patient Survival

Table 1. Distribution, Key Demographic and Outcome Statistics of Patients Initiating Antiretroviral Treatment 2003 to 2008 in the 29 Sites in East Africa.

	No. (% or Min-Max)
Patient Population by Country	
Kenya	33,586 (74.1)
Uganda	9,737 (21.5)
Tanzania	2,018 (4.4)
Patient Population by Site Type	
Health Center/Clinic	9,539 (21.0)
District/Provincial Hospital	17,244 (38.0)
Teaching/National Referral Hospital	18,558 (40.9)
Patient by Year of ART Initiation	
2003	689 (1.5)
2004	3,012 (6.6)
2005	9,169 (20.2)
2006	10,931 (24.1)
2007	12,776 (28.2)
2008	8,764 (19.3)
Median Age at ART Initiation	37 (18-88)
Female Patients	29,118 (64.3)
Median Survival Time (months)	14.2 (0-75.6)
Total person-time of observation (months)	809,860
Documented Deaths	3,082 (6.8)
Lost to Follow-up	13,253 (29.2%)

Table 2. Key Characteristics of the 29 Sites in East Africa and Attributes of their Respective Patient Population.

Site (N=29)	Country	Site Type	Population Served	ǂNo. of ART Patients (N=47,518)	Year of ART Initiation	Median Age at ART Initiation	Percent Female
EA01	Kenya	District/ Provincial Hospital	In-between Urban/rural	3993	2003-2008	36 (18-88)	66.0
EA02	Kenya	Health Center/Clinic	Mainly Urban	172	2007-2008	35 (20-69)	62.9
EA03	Kenya	Health Center/Clinic	Mainly Urban	94	2007-2008	29 (19-49)	100.0
EA04	Kenya	Teaching/ National Referral Hospital	Mainly Urban	8592	2003-2008	37 (18-81)	58.7
EA05	Kenya	District/Provincial Hospital	In-between Urban/rural	324	2005-2008	39 (19-70)	73.2
EA06	Kenya	District/Provincial Hospital	In-between Urban/rural	583	2006-2008	38 (20-75)	66.6
EA07	Kenya	District/Provincial Hospital	In-between Urban/rural	322	2006-2008	38 (19-61)	66.2
EA08	Kenya	District/Provincial Hospital	In-between Urban/rural	788	2004-2008	37 (19-79)	65.5

Note: ǂNumber of patients who started ART by Dec. 2008

Table 2 (Cont'd). Key Characteristics of the 29 Sites in East Africa and Attributes of their Respective Patient Population.

Site (N=29)	Country	Site Type	Population Served	ǂNo. of ART Patients (N=47,518)	Year of ART Initiation	Median Age at ART Initiation	Percent Female
EA09	Kenya	District/Provincial Hospital	Mainly Urban	2023	2004-2008	38 (18-74)	70.0
EA10	Kenya	Health Center/Clinic	Mainly Rural	891	2007-2008	38 (20-78)	65.5
EA11	Kenya	Health Center/Clinic	In-between Urban/rural	2004	2004-2008	38 (18-75)	65.1
EA12	Kenya	Health Center/Clinic	Mainly Rural	788	2004-2008	38 (19-77)	62.4
EA13	Kenya	District/Provincial Hospital	Mainly Urban	2443	2006-2008	37 (18-81)	64.5
EA14	Kenya	District/Provincial Hospital	Mainly Urban	142	2007-2008	35 (20-62)	64.1
EA15	Kenya	Health Center/Clinic	In-between Urban/rural	1343	2004-2008	37 (19-76)	66.8
EA16	Kenya	Health Center/Clinic	Mainly Urban	2781	2003-2008	38 (18-76)	64.7

Note: ǂNumber of patients who started ART by Dec. 2008

Table 2 (Cont'd). Key Characteristics of the 29 Sites in East Africa and Attributes of their Respective Patient Population.

Site (N=29)	Country	Site Type	Population Served	ǂNo. of ART Patients (N=47,518)	Year of ART Initiation	Median Age at ART Initiation	Percent Female
EA17	Kenya	District/Provincial Hospital	Mainly Urban	2933	2005-2008	38 (18-80)	68.1
EA18	Kenya	District/Provincial Hospital	In-between Urban/rural	538	2005-2008	36 (19-77)	62.5
EA19	Kenya	Health Center/Clinic	Mainly Urban	782	2007-2008	33 (18-72)	66.8
EA20	Kenya	Health Center/Clinic	Mainly Urban	55	2007-2008	21 (18-25)	77.1
EA21	Kenya	District/Provincial Hospital	In-between Urban/rural	1080	2006-2008	36 (18-77)	62.6
EA22	Kenya	Health Center/Clinic	Mainly Rural	629	2004-2008	38 (18-78)	68.8
EA23	Kenya	District/Provincial Hospital	Mainly Urban	286	2003-2008	30 (18-57)	73.4
EA27	Tanzania	Teaching/National Referral Hospital	Mainly Urban	607	2005-2008	40 (18-82)	61.0

Note: ǂNumber of patients who started ART by Dec. 2008

Table 2 (Cont'd). Key Characteristics of the 29 Sites in East Africa and Attributes of their Respective Patient Population.

Site (N=29)	Country	Site Type	Population Served	ǂNo. of ART Patients (N=47,518)	Year of ART Initiation	Median Age at ART Initiation	Percent Female
EA28	Tanzania	District/Provincial Hospital	Mainly Urban	1411	2005-2008	38 (19-82)	65.4
EA30	Uganda	Teaching/National Referral Hospital	Mainly Urban	339	2003-2008	32 (18-52)	69.6
EA32	Uganda	Teaching/National Referral Hospital	Mainly Rural	1363	2007-2008	35 (18-80)	60.5
EA33	Uganda	District/Provincial Hospital	Mainly Urban	378	2003-2008	32 (19-71)	68.8
EA34	Uganda	Teaching/National Referral Hospital	Mainly Urban	7657	2003-2008	36 (18-80)	64.2

Note: ǂNumber of patients who started ART by Dec. 2008

Table 3. Classification of the 29 Sites by Active Screening Entry Points based on Primary and Secondary Source of Patients.

Site (N=29)	Primary Source of Patients	Secondary Source of Patients	Site has Primarily Active Screening Entry Points
EA01	Provider Initiated Testing and Counseling	Voluntary Counseling and Testing (directly)	Yes
EA02	Voluntary Counseling and Testing (via Referral)	Voluntary Counseling and Testing (directly)/Other (Transfer In) [tied]	Yes
EA03	Voluntary Counseling and Testing (directly) and (via Referral)[tied]	Provider Initiated Testing and Counseling	Yes
EA04	Provider Initiated Testing and Counseling	Inpatient Wards	No
EA05	Provider Initiated Testing and Counseling	Prevention of Mother to Child Transmission Program within the Antenatal Clinic	Yes
EA06	Voluntary Counseling and Testing (directly)	Voluntary Counseling and Testing (via Referral)	Yes
EA07	Inpatient Wards	Provider Initiated Testing and Counseling	No
EA08	Voluntary Counseling and Testing (directly)	Provider Initiated Testing and Counseling	Yes

Table 3 (Cont'd). Classification of the 29 Sites by Active Screening Entry Points based on Primary and Secondary Source of Patients.

Site (N=29)	Primary Source of Patients	Secondary Source of Patients	Site has Primarily Active Screening Entry Points
EA09	Voluntary Counseling and Testing (directly)	Prevention of Mother to Child Transmission Program within the Antenatal Clinic	Yes
EA10	Voluntary Counseling and Testing (directly)	Provider Initiated Testing and Counseling	Yes
EA11	Prevention of Mother to Child Transmission Program within the Antenatal Clinic	Voluntary Counseling and Testing (directly)	Yes
EA12	Voluntary Counseling and Testing (via Referral)	Provider Initiated Testing and Counseling	Yes
EA13	Voluntary Counseling and Testing (directly)	Voluntary Counseling and Testing (via Referral)	Yes
EA14	Voluntary Counseling and Testing (directly)	Tied between Provider Initiated Testing and Counseling and TB Clinic followed by Voluntary Counseling and Testing (directly)	Yes
EA15	Provider Initiated Testing and Counseling	TB Clinic	No

Table 3 (Cont'd). Classification of the 29 Sites by Active Screening Entry Points based on Primary and Secondary Source of Patients.

Site (N=29)	Primary Source of Patients	Secondary Source of Patients	Site has Primarily Active Screening Entry Points
EA16	Provider Initiated Testing and Counseling	Voluntary Counseling and Testing (directly)	Yes
EA17	Provider Initiated Testing and Counseling	Prevention of Mother to Child Transmission Program within the Antenatal Clinic	Yes
EA18	Inpatient Wards	Voluntary Counseling and Testing (directly)	No
EA19	Voluntary Counseling and Testing (directly)	Voluntary Counseling and Testing (via Referral)/ Other (Research)[tied]	Yes
EA20	Voluntary Counseling and Testing (directly)	Prevention of Mother to Child Transmission Program within the Antenatal Clinic	Yes
EA21	Voluntary Counseling and Testing (directly)	Prevention of Mother to Child Transmission Program within the Antenatal Clinic	Yes
EA22	Outpatient Ward	Inpatient Wards	No

Table 3 (Cont'd). Classification of the 29 Sites by Active Screening Entry Points based on Primary and Secondary Source of Patients.

Site (N=29)	Primary Source of Patients	Secondary Source of Patients	Site has Primarily Active Screening Entry Points
EA23	Voluntary Counseling and Testing (directly)	Provider Initiated Testing and Counseling	Yes
EA27	Provider Initiated Testing and Counseling	Prevention of Mother to Child Transmission Program within the Antenatal Clinic	Yes
EA28	Voluntary Counseling and Testing (directly)	Prevention of Mother to Child Transmission Program within the Antenatal Clinic	Yes
EA30	Prevention of Mother to Child Transmission Program within the Antenatal Clinic	Voluntary Counseling and Testing (directly)	Yes
EA32	Voluntary Counseling and Testing (directly)	Outpatient Ward	No
EA33	Provider Initiated Testing and Counseling	Voluntary Counseling and Testing (directly)/Prevention of Mother to Child Transmission Program within the Antenatal Clinic[tied]	Yes

Table 3 (Cont'd). Classification of the 29 Sites by Active Screening Entry Points based on Primary and Secondary Source of Patients.

Site (N=29)	Primary Source of Patients	Secondary Source of Patients	Site has Primarily Active Screening Entry Points
EA34	Prevention of Mother to Child Transmission Program within the Antenatal Clinic	Inpatient Wards	No

Figure 1. Crude Kaplan-Me+ier Survival Curves Comparing Patients in Active Screening Entry Points Sites (blue) with Patients in Non-Active Screening Entry Point Sites (red).

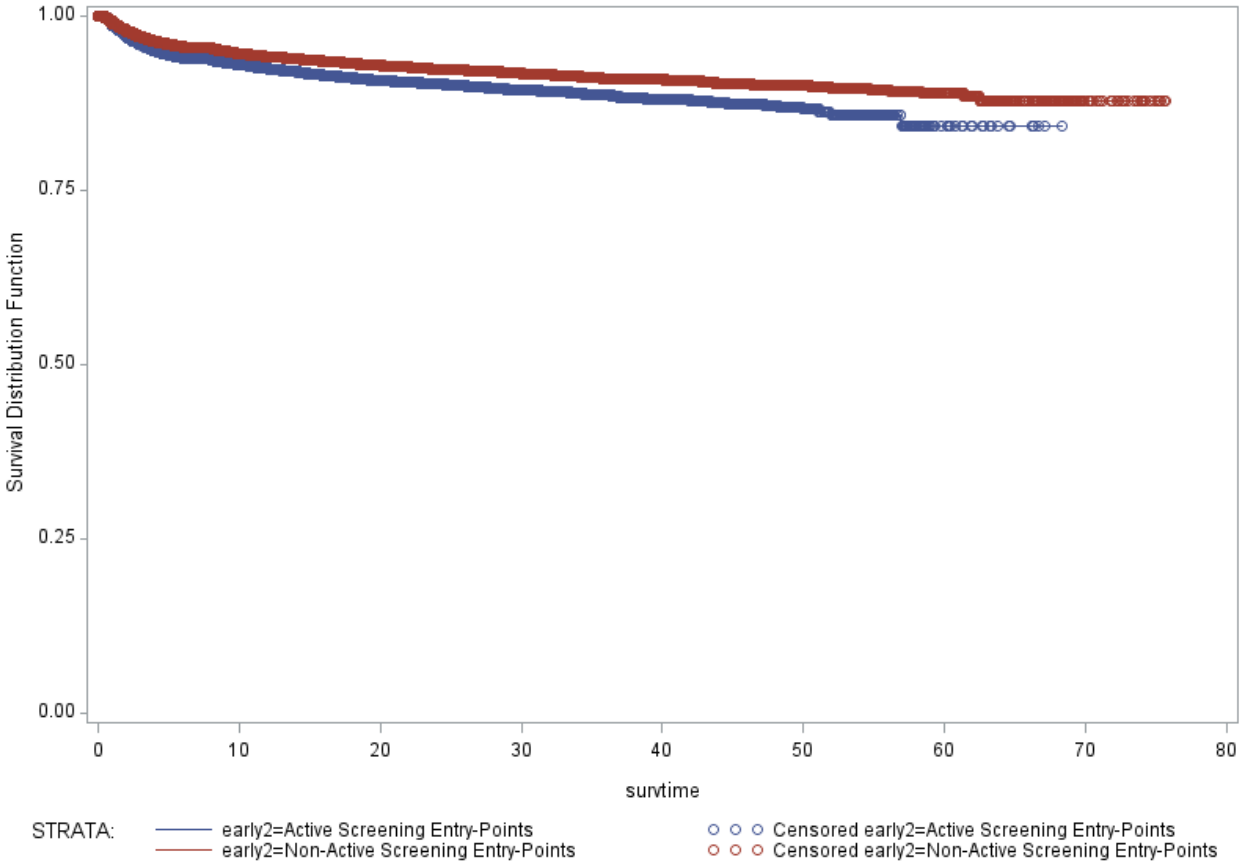


Table 4. Distribution of Potential Confounders and Associations with Active Screening Entry Points (Exposure) and Patient Survival (Outcome).

	Sites with Active Screening Entry Points N (%)	Sites without Active Screening Entry Points N (%)	Association with the Exposure OR (P-value[1])	Association with the Outcome HR (P-value)
Patient-level Characteristics				
Number of Patients	24,725 (100)	20,616 (100)	--	--
Male Sex	8,348 (33.8)	7,845 (38.1)	0.84 (<0.09)	1.54 (<0.0001)
Site and Programmatic-level Level Characteristics				
Number of Sites	21 (100)	8 (100)	--	--
Sites by Type				
Health Center/Clinic	7 (33.3)	3 (37.5)	0.39 (0.61)	1.05 (0.78)
District/Provincial Hospital	12 (57.1)	2 (25)	Reference	Reference
Teaching/National Referral Hospital	2 (9.5)	3 (37.5)	0.11 (0.08)	0.64 (0.0002)
Site Patient-Provider Ratio				
0.0 to 4.0	5 (23.8)	1 (12.5)	1.67 (1.00)	0.34 (<0.0001)
4.01 to 8.5	5 (23.8)	3 (37.5)	0.56 (1.00)	0.86 (0.57)
8.6 to 11.99	6 (28.6)	2 (25)	Reference	Reference
12.0 to 35.53	5 (23.8)	2 (25)	0.83 (1.00)	0.77 (0.13)
Sites with a Waiting List	3 (14.3)	3 (37.5)	0.28 (0.30)	0.79 (0.05)

Table 4 (Cont'd). Distribution of Potential Confounders and Associations with Active Screening Entry Points (Exposure) and Patient Survival (Outcome).

	Sites with Active Screening Entry Points N (%)	Sites without Active Screening Entry Points N (%)	Association with the Exposure OR (P-value[1])	Association with the Outcome HR (P-value)
Patient Population Served Predominantly				
Urban Patients	13 (61.9)	3 (37.5)	Reference	Reference
Rural Patients	2 (9.5)	2 (25)	0.23 (0.25)	1.65 (0.05)
In between Urban/Rural	6 (28.6)	3 (37.5)	0.46 (0.63)	1.59 (0.0001)
Site's ART Eligibility Criterion for Patients in WHO Clinical Stage 1 or 2 (<200 vs 200+ cells/μL)	16 (76.2)	5 (62.5)	1.92 (0.65)	1.42 (0.03)

[1]Fisher's Exact Test used due to expected cell values < 5.

Table 5. Hazard Ratios (HR) and 95% Confidence Intervals for Active Screening Entry-Point (ASEP) Cox Models: 1) Crude Model, 2) Patient Factors Only Adjusted Model, 3) Programmatic Factors Only Adjusted Model, and 4) Patient and Programmatic Factors Adjusted Models (with and without "presence of a waiting list").

Parameter	Model 1: Crude HR (95% CI)	Model 2: Adj. for for Patient Factors HR (95% CI)	Model 3: Adj. for Programmatic Factors HR (95% CI)	Model 4: Adj. for for Patient and Programmatic Factors HR (95% CI)	Model 5: Adj. for Patient and Programmatic Factors HR (95% CI)
Active Screening Entry Points (Yes vs. No)	1.32 (1.03-1.70)	1.35 (1.04-1.75)	0.83 (0.65-1.07)	0.83 (0.63-1.09)	0.82 (0.64-1.06)
Sex (Male vs Female)	---	1.56 (1.43-1.71)	---	1.58 (1.46- 1.71)	1.58 (1.46-1.71)
Sites by Type					
Health Center/Clinic vs District/Provincial Hospitals	---	---	1.02 (0.78-1.33)	0.99 (0.76-1.29)	1.02 (0.78-1.33)
Teaching/National Referral Hospital vs District/Provincial Hospitals	---	---	0.54 (0.34-0.84)	0.51 (0.32- 0.82)	0.51 (0.32-0.80)
Site Patient-Provider Ratio					
0-4.0 vs 8.6-11.99	---	---	0.42 (0.27-0.67)	0.35 (0.23- 0.53)	0.40 (0.25-0.64)
4.01-8.5 vs 8.6-11.99	---	---	0.98 (0.69-1.40)	0.96 (0.68- 1.34)	0.99 (0.69-1.41)

Table 5 (Cont'd). Hazard Ratios (HR) and 95% Confidence Intervals for Active Screening Entry-Point (ASEP) Cox Models: 1) Crude Model, 2) Patient Factors Only Adjusted Model, 3) Programmatic Factors Only Adjusted Model, and 4) Patient and Programmatic Factors Adjusted Models (with and without "presence of a waiting list").

Parameter	Model 1: Crude HR (95% CI)	Model 2: Adj. for for Patient Factors HR (95% CI)	Model 3: Adj. for Programmatic Factors HR (95% CI)	Model 4: Adj. for for Patient and Programmatic Factors HR (95% CI)	Model 5: Adj. for Patient and Programmatic Factors HR (95% CI)
Site Patient-Provider Ratio					
12-35.33 vs 8.6-11.99	---	---	1.13 (0.84-1.52)	1.09 (0.83- 1.45)	1.14 (0.84-1.53)
Patient Waiting List (Yes vs No)	---	---	1.23 (0.78-1.95)	---	1.24 (0.77-1.97)
Predominant Patient Population Served					
Rural vs Urban	---	---	1.48 (0.98-2.22)	1.46 (0.96- 2.21)	1.47 (0.97-2.22)
In Between Urban/Rural vs Urban	---	---	1.24 (0.89-1.71)	1.21 (0.88- 1.67)	1.23 (0.89-1.71)
Site's ART Eligibility Criterion for Patients in WHO Clinical Stage 1 or 2 (<200 vs 200+ cells/μL)	---	---	1.10 (0.67-1.81)	0.88 (0.71-1.10)	1.08 (0.65-1.79)

Figure 2. Adjusted Survival Curves Comparing Patients in Active Screening Entry Points Sites (blue) with Patients in Non-Active Screening Entry Point Sites (red).

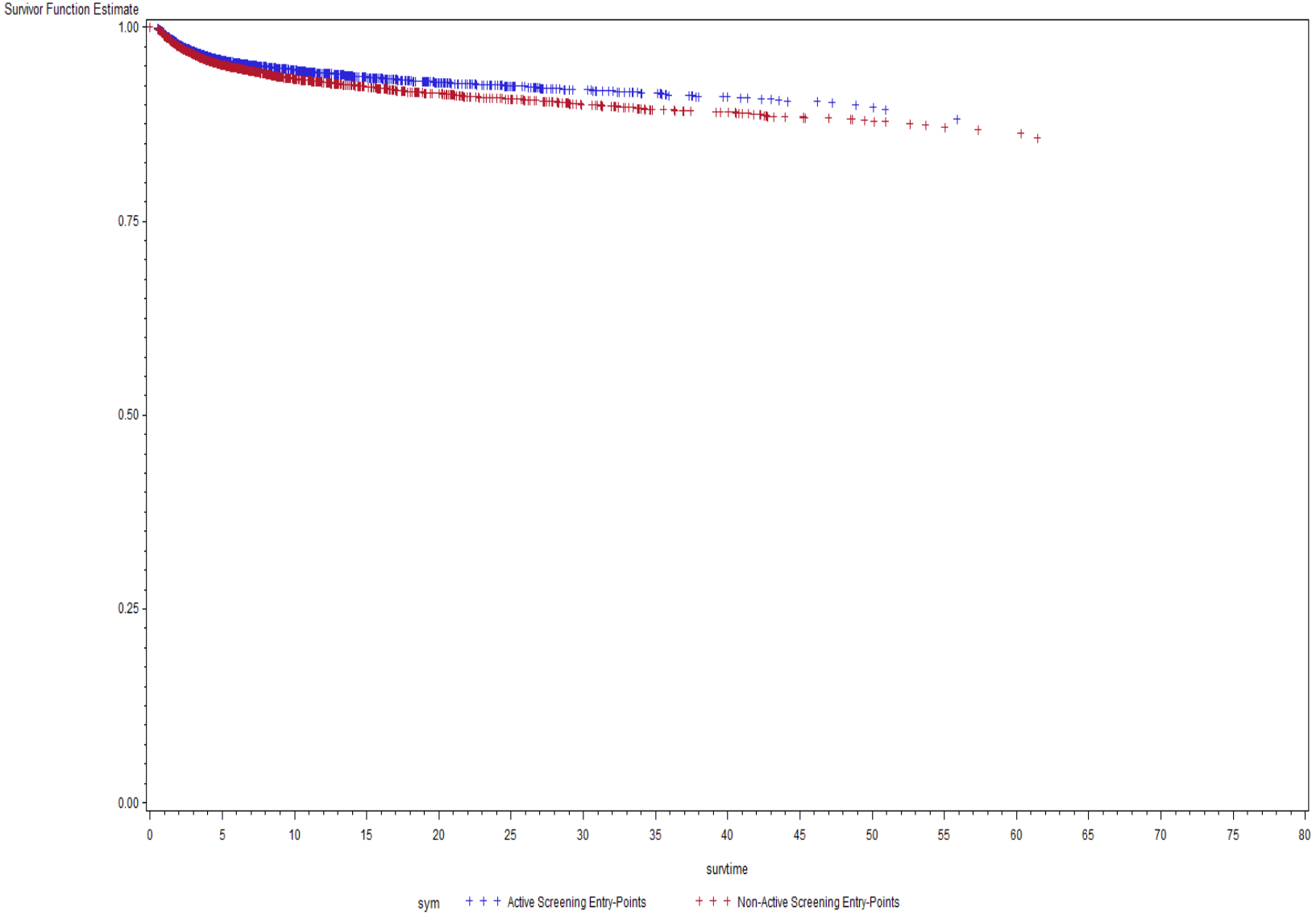


Table 6. Crude Association Between the Exposure (Active Screening Entry Points (ASEP)) and the Potential Mediator (CD4 Cell Count at ART initiation) and the Potential Mediator (CD4 Cell Count at ART Initiation) and Outcome (Patient Survival).

	Mean CD4 at ART Initiation	**P-Value**
Association Between Exposure and Mediator		
Active Screening Entry Point Sites	104.57	Reference
Non-Active Screening Entry Point Sites	84.93	0.03
	HR	**P-Value**
Association Between Mediator and Outcome		
LogCD4 (all sites)	0.64	<0.0001
LogCD4[1] (ASEP sites only)	0.64	<0.0001
LogCD4[1] (non-ASEP sites only)	0.63	<0.0001

[1]CD4 is modeled with a time-dependent covariate (logCD4*survival) to meet the proportional hazard assumption. HR accounts for this covariate.

Table 7. Test for Mediation by CD4 Cell Count at ART Initiation Using Final Active Screening Entry Point Model (Model 5).

Parameter	Model 5 (Final Model) Beta Estimate HR (95% CI)	Model 5 with Potential Mediator Beta Estimate HR (95% CI)
Active Screening Entry Points (Yes vs. No)	-0.19605 0.82 (0.64-1.06)	-0.06916 0.93 (0.75-1.16)
Sex (Male vs Female)	0.45580 1.58 (1.46-1.71)	0.33020 1.39 (1.25-1.55)
Sites by Type		
Health Center/Clinic vs District/Provincial Hospitals	0.02041 1.02 (0.78-1.33)	-0.08532 0.92 (0.70-1.21)
Teaching/National Referral Hospital vs District/Provincial Hospitals	-0.67071 0.51 (0.32-0.80)	-0.55723 0.57 (0.39-0.84)
Site Patient-Provider Ratio		
0-4.0 vs 8.6-11.99	-0.91727 0.40 (0.25-0.64)	-0.68753 0.50 (0.32-0.82)
4.01-8.5 vs 8.6-11.99	-0.01561 0.99 (0.69-1.41)	0.11059 1.12 (0.82-1.53)
12-35.33 vs 8.6-11.99	0.12785 1.14 (0.84-1.53)	0.06884 1.07 (0.79-1.46)

Table 7 (Cont'd). Test for Mediation by CD4 Cell Count at ART Initiation Using Final Active Screening Entry Point Model (Model 5).

Parameter	Model 5 (Final Model) Beta Estimate HR (95% CI)	Model 5 with Potential Mediator Beta Estimate HR (95% CI)
Patient Waiting List (Yes vs No)	0.21201 1.24 (0.77-1.97)	0.12268 1.13 (0.73-1.76)
Predominant Patient Population Served		
Rural vs Urban	0.38651 1.47 (0.97-2.22)	0.48977 1.63 (1.14-2.34)
In Between Urban/ Rural vs Urban	0.20696 1.23 (0.89-1.71)	0.23415 1.26 (0.93-1.73)
Site's ART Eligibility Criterion for Patients in WHO Clinical Stage 1 or 2 (<200 vs 200+ cells/μL)	0.07417 1.08 (0.65-1.79)	0.17030 1.19 (0.74-1.90)
Age (years)		
18-23 vs. 30-35	---	0.18803 1.21 (0.84-1.73)
24-29 vs. 30-35	---	0.01926 1.02 (0.91-1.15)
36-41 vs. 30-35	---	-0.01075 0.99 (0.88-1.11)
42-47 vs. 30-35	---	0.05409 1.06 (0.88-1.26)

Table 7 (Cont'd). Test for Mediation by CD4 Cell Count at ART Initiation Using Final Active Screening Entry Point Model (Model 5).

Parameter	Model 5 (Final Model) Beta Estimate HR (95% CI)	Model 5 with Potential Mediator Beta Estimate HR (95% CI)
Age (years)		
48-53 vs. 30-35	---	0.19145 1.21 (1.07-1.37)
54-59 vs. 30-35	---	0.17452 1.19 (0.99-1.43)
60-65 vs. 30-35	---	0.24358 1.28 (0.96-1.69)
66-88 vs. 30-35	---	0.58152 1.79 (1.30-2.48)
LogCD4[1]	---	-0.47051 0.63 (0.60-0.65)

[1]LogCD4: potential mediator; modeled as a time dependent variable to meet the Proportional Hazard Assumption for LogCD4

Directed Acyclical Graphs

Active Screening Entry Points – Patient Survival

Figure 3. Directed Acyclical Graph for Entry Points Survival Model with Hypothesized Associations.

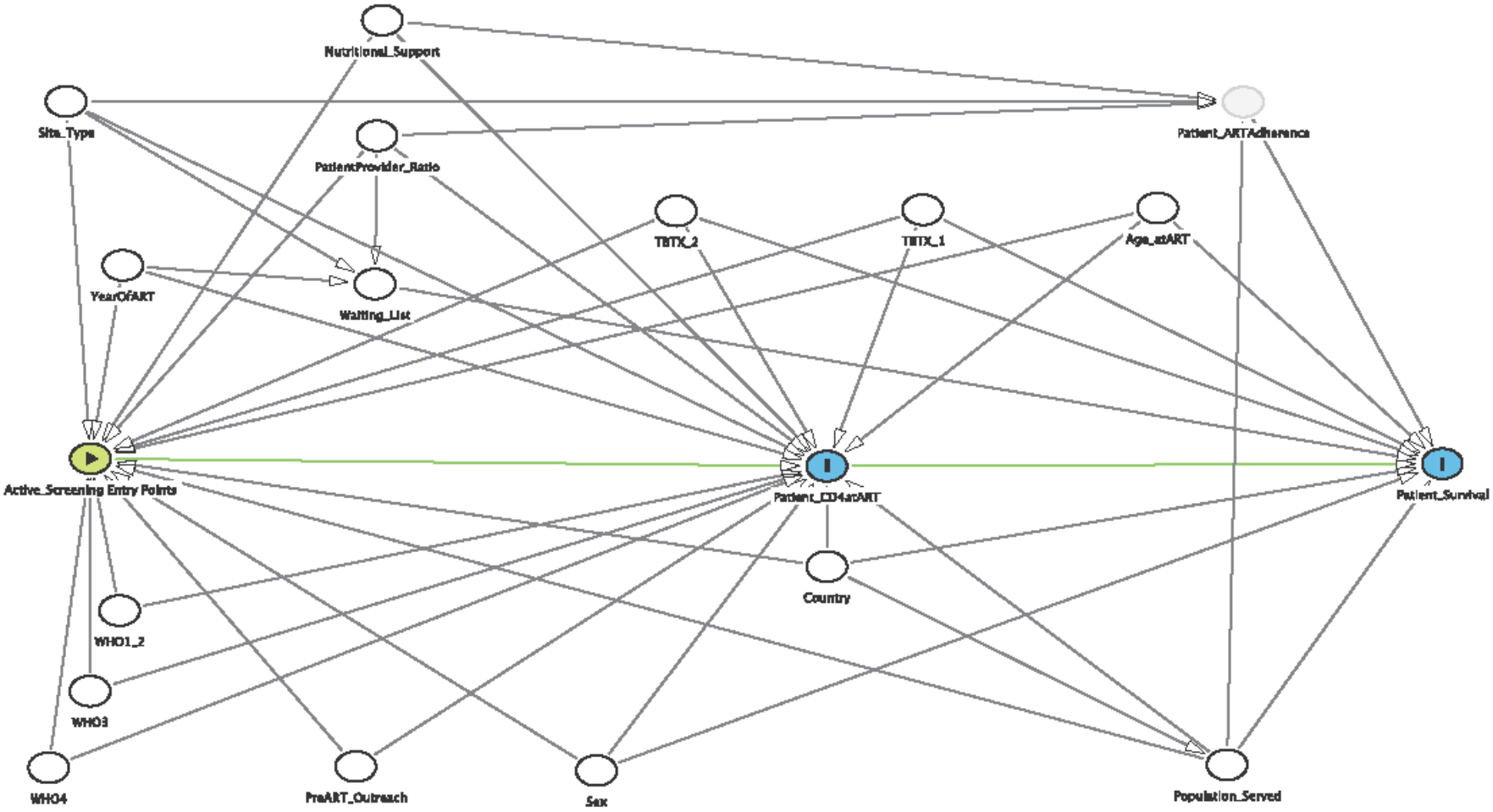
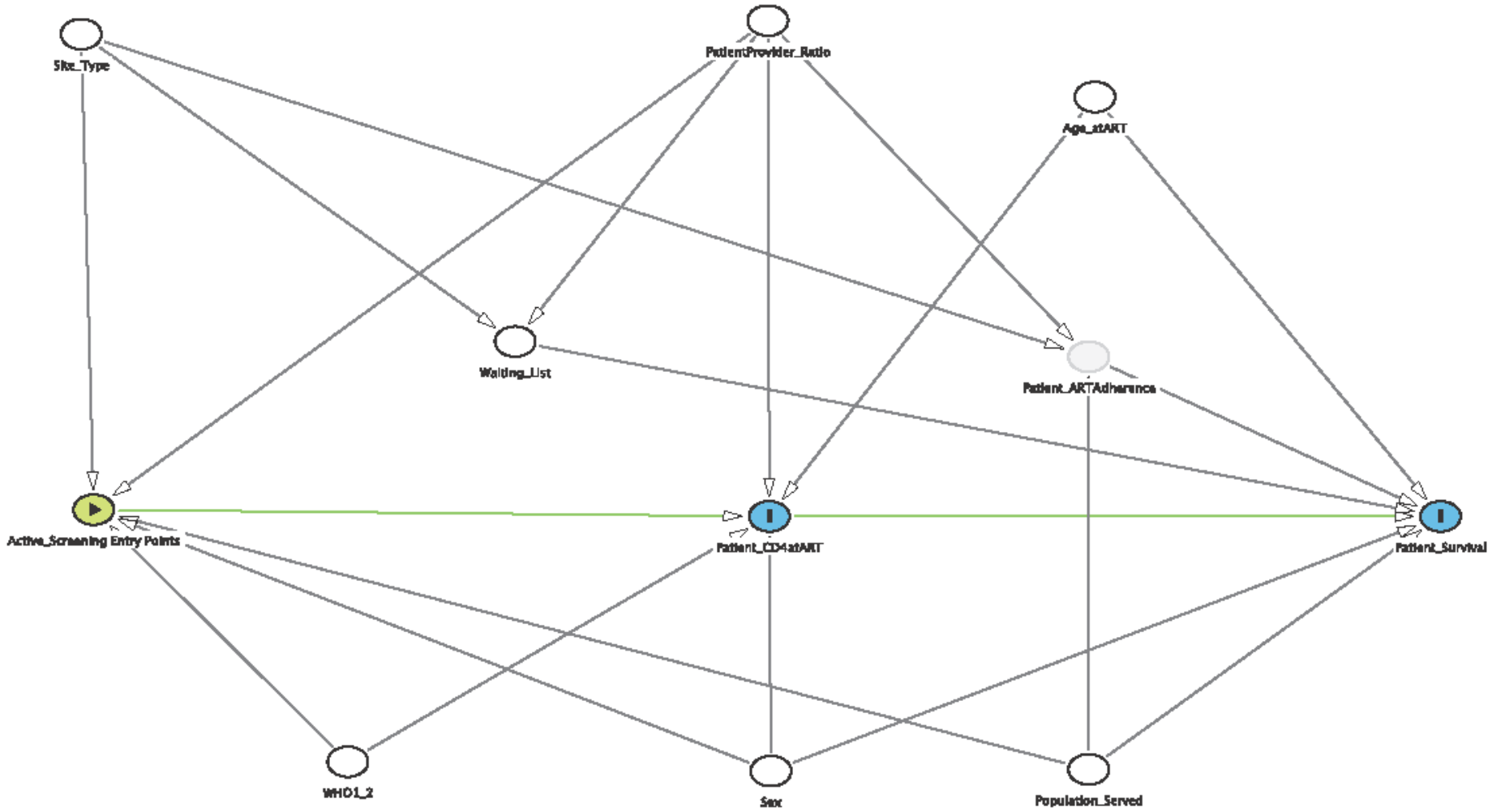


Figure 4. Directed Acyclical Graph for Entry Points Survival Model Following Testing of Hypothesized Associations.



Chapter 5. Conclusions

Conclusions

Objectives

The central aims of this dissertation were to:

1) critically review and synthesize the literature examining individual-, programmatic-, and societal-level barriers to HIV testing, enrollment into pre-ART care, and ART initiation;
2) examine the association between patient CD4 cell count at ART initiation and the conduct of active screening at HIV/AIDS care and treatment sites;
3) examine the association between patient CD4 cell count at ART initiation and sites with primarily active screening entry points;
4) examine the association between patient survival and sites with primarily active screening entry points;
5) examine patient CD4 cell count at ART initiation as a mediator of the association between patient survival and active screening entry points.

Summary of Results

In Chapter 2, I conducted a critical review of the literature to identify barriers to ART initiation along the HIV treatment cascade. The findings identified:

1) individual, programmatic and societal-level barriers to HIV testing, enrolling into care, and ART initiation;

2) barriers pertaining to lack of knowledge of HIV/AIDS and ART (e.g. HIV/AIDS symptomatology, ART benefits, ART toxicity), limited accessibility to services, poor quality of services, shortage of staff, and HIV-related stigma as the most prominent.

In Chapter 3, I performed separate analyses to tests the association between the exposures "Active Screening" and "Active Screening Entry Points" with the outcome patient CD4 cell count at ART initiation. The result showed that patients in sites with predominantly "Active Screening Entry Points" initiate ART, on average, with CD4 cell counts 24 cells/μL higher than patients in sites with mainly "non-Active Screening Entry Points." The analyses in Chapter 4, assessed the relationship between "Active Screening Entry Points" and survival, and whether this relationship was mediated by patient CD4 cell count at ART initiation. The findings failed to show a statistically significant difference in survival between patients in sites with and without "Active Screening Entry Points" [HR (95% CI): 0.82 (0.64 – 1.06)] though the association was in the expected direction.

Key Strengths and Limitations

This dissertation has some limitations. Given the nature of qualitative studies, we cannot determine the extent to which the barriers identified hinder progression through the stages of the treatment cascade. Though results from quantitative studies can help shed light on this matter, the ones identified were cross-sectional in nature and thus should be interpreted with caution.

The classification of entry points as active or non-active screening was based on how these HIV related services have operated historically and not based on a detailed response on a survey. Nonetheless, for entry points such as Provider Initiated Testing and Counseling and Prevention of Mother-to-Child Transmission active screening has always been a defining characteristic of these programs while for others, such as TB clinics, it was not the norm at the time of this study. Lastly, the programmatic and site level data collected through the IeDEA Site Assessment Tool reflects information at one point in time which may not be indicative of conditions present during the entire follow-up period.

There are several strengths to the studies in this dissertation. The articles identified in the literature review covered the four different regions which carry the biggest burden of the HIV epidemic. Studies from sub-Saharan Africa, the region with the highest HIV-prevalence, and South Africa, the country with the largest number of people living with HIV, were well-represented. The years of publication of the articles (2001 to 2012) coincide with the period when major scale-up of ART occurred in low- and middle-income countries. To my knowledge, we present the first study investigating the relationship between active screening and survival. The dataset has a respectable number of sites each with a considerable number of ART patients. The sites were from diverse geographic settings and data collection extended over several years. Patient, programmatic and contextual level variables were considered for statistical adjustment. Finally, given the nature of the data collection the results represent real world conditions.

Public Health Relevance

We have yet to reach the point when we can recognize the accomplishments of ART scale-up without strongly emphasizing remaining challenges. The initiation of treatment in the advanced stages of the infection is a major factor undermining the global efforts on the HIV epidemic [15]. Late ART initiation is more of a reflection of the deficiencies in providing healthcare to populations in low- and middle-income countries than an individual's determination to access ART at the appropriate time.

The HIV epidemic has shone a spotlight on the neglected healthcare systems of low- and middle-income countries. This neglect is reflected by the observation that most of the identified barriers to ART initiation are somehow related to lack of continuity, affordable, good quality healthcare. Chronic conditions like HIV require continuous testing of those without the virus as well uninterrupted monitoring of those with the virus. Therefore, unless the limitations of the healthcare system are considered, interventions addressing late ART initiation will be undermined. This may be the case for active screening as a means to combat late ART initiation.

Although the results in Chapters 3 show a CD4 cell count advantage for patients in "Active Screening Entry-Points", the mean CD4 cell count of these patients are well-below all of the World Health Organization ART guidelines underlining both the severity and complexity of late ART initiation in these settings [41, 43, 44, 53]. Given that most patients in the study population started treatment at advanced stages of the infection, it is not surprising that a considerable difference in survival was not detected. These results are likely a reflection of the failure of the healthcare system rather than active screening. If there is limited or no contact between providers and patients before HIV progresses to AIDS, providers will not have the

opportunity to initiate testing during this critical period even if they are fully compliant with active screening.

It is unlikely that the limitations of healthcare systems in low- and middle-income countries will be addressed in the upcoming decades. This reality should encourage public health institutions to promote comprehensive, multifaceted interventions which consider the context in which they are to be applied. The fact that under real world condition the results show that active screening leads to a moderate increase in CD4 cell count at ART initiation is promising. In addition, the demonstrated benefits of active screening (e.g. high acceptability, increased number of patients tested and higher rate of identification of previously undiagnosed people living with HIV) merit adoption of this intervention particularly in regions with a high HIV burden and where a low proportion of the population is aware of their HIV status. To become effective in improving survival, the implementation of active screening programs in low- and middle-income countries may require a systematic shift to a more preventative approach to healthcare with improved referral mechanism to efficiently bring those in need into treatment. This will increase the opportunities for practitioners to identify HIV-positive individuals earlier in the infection.

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Appendix A

Methodological Details

Methodological Details: Chapter 2 (Literature Review: Barriers to ART Initiation)

Search Strategy

PubMed, Eric and Popline were considered but not included in this review. PubMed would have provided the same information as Ovid Medline but only on a different interface. The focus of Eric and Popline databases, education and international reproductive health, respectively, are not directly in line with the focus of this search.

Methodological Details: Chapter 3 (Active Screening – CD4 Cell Count at ART Initiation)

Measures

Exposure Variables

The patient date of enrollment and the date active screening was initiated at the site were used to calculate the percentage of patients who enrolled into care after active screening commenced. When the day and/or month were missing from the start date of active screening, the middle of the month (15) and year (June) were used to complement the year. Among 27 sites reporting information on active screening, none reported the day and 17 did not report the month for the date active screening began. Patients enrolling into care at least one day following the start of active screening were counted in the proportion of who enrolled after active screening began.

Potential Confounders:

Patient-level Variables

Following the assessment for linearity (see below for details), age at ART initiation was operationalized as a set of equally spaced indicator variables of five-year intervals ranging from age 18 to 88 years. Measures of socio-economic status (years of school completed, highest

education level achieved, availability of electricity and piped water in the home, monthly income) could not be considered for statistical adjustment due to the high proportion of missing values.

Programmatic-level Variables

ART Eligibility Criteria

The sites' CD4 cell count criterion for ART initiation at each WHO stage was analyzed using a set of three indicator dichotomous variables: 1) for WHO clinical stages 1 and 2, sites using a CD4 count threshold of less than 200 cells/μL to initiate ART for patients with this clinical stage were compared with those using CD4 counts of 200 cells/μL or more; 2) for WHO clinical stage 3, sites using a CD4 count threshold of less than 350 cells/μL to initiate ART for patients with this clinical stage were compared with those using CD4 counts of 350 cells/μL or more; 3) for WHO clinical stage 4, sites using a CD4 count threshold of less than 250 cells/μL to initiate ART for patients with this clinical stage were compared with those using CD4 counts of 250 cells/μL or more.

Patient-provider ratio

Patient-provider ratio was calculated for each site as the total number of patients on ART during the first quarter of 2008 divided by the total number of days providers are available. The first quarter of 2008 was chosen because it was the time closest to when 1) the provider information was collected and 2) all the sites had patients on ART. Note that category 12-35.53 was made considerably wider compared with the other three (ratios 0-4.0, 4.01-8.5, 8.6-11.99) to include the outlier value of 35.52; otherwise the range would have only extended to 18.54. Selection of the categories was based on the objective of dividing the sites into subgroups each

with an equal number of sites of similar patient-provider ratios to minimize residual confounding [141].

*Fees for Services, ARV Stockouts, Frequency of CD4 Cell Monitor*ing

Since there was virtually no variability in the responses, the following constructs were not considered for statistical adjustment: charging fees for services rendered (laboratory tests, first line ART, opportunistic infection prophylaxis, opportunistic infection treatment, routine follow-up care, and transportation to the clinic), experiencing ARV disruptions, frequency of CD4 cell count monitoring.

Site-level Variables

Site Classification

Sites were also classified as private or public. Due to a small number of private sites, this variable was not considered for statistical adjustment.

Statistical Analysis

Justification for the Use of Mixed Linear Regression Models and Assessment of Statistical Assumptions

Due to the subject matter of this dissertation (an infectious disease that tends to cluster in space and time), and the substantial grouping of patients into sites (up to 8,500 in one of the sites) it is likely that the degree of clustering leads to underestimated standard errors necessitating the need for regression models, such as random effects models, that take clustering into account. In addition to the latter points, I also calculated the intraclass correlation (ICC) by fitting an unconditional means model to assess the degree of clustering. The statistical significance of the ICC was calculated by $F_{g-1(\text{numerator df}),\ g(k-1)(\text{denominator df})}=1+(k-1)ICC/1-ICC$;

where g=the number of groups and k=the number of subjects in each group [142]. The average number of subjects per site was 1,563 with a minimum per site of 54.

The estimated ICC was 0.035 [0.05207/(1.4175+0.05207)] with an AIC of 120766.3. Even when k=54, the p-value for F-statistic 2.96 [1+53(0.035)/(1-0.035)] with degrees of freedom 28 and 1,537 (29*53) is less than 0.05. The AIC for the unconditional model without the random intercept is 120933.5. Given the size and statistical significance of the ICC, the large number of subjects per cluster (range: 55 to 8,592), that infectious diseases like HIV tend to cluster in space and time, and the view by some statisticians that when the number of subjects in a group is large even ICC less than 0.1 can influence significance tests [142], the clustering in the data could not be ignored. Mixed models with random intercepts were fitted to account for the clustering [118] though Generalized Estimating Equation models also would have been appropriate.

The linearity assumption for continuous variables patient-provide ratio and age at ART initiation was assessed separately for each variable using two approaches. We fitted a model with both a continuous and a squared-term version of the covariate and tested the statistical significance (using alpha = 0.05) of the squared-terms. Secondly, we fitted a bivariable Cox model of the outcome and covariate. Patient-provider ratio was modeled using three indicator variables for the four categories created for this variable (0-4.0, 4.01-8.5, 8.6-11.99 (reference group), and 12-35.53), and age at ART initiation using eight indicator variables of five-year increments for the nine categories (18-23; 24-29; 30-35 (reference group)…66-88). The estimated beta estimates for the indicator variables were plotted and assessed for evidence of a linear pattern. Based on the results of these assessments, patient-provider ratio and age at ART initiation were operationalized using three and eight indicator variables, respectively. Lastly,

model assumptions including normality and homogeneity of variance of the level-1 and level-2 errors were assessed using the macro "Mixed_DX" [143]. Outside the violation of normality, which was addressed through a log transformation of the patient CD4 cell count at ART initiation, there were no substantial violation of homogeneity of variance for the level-1 or level-2 errors.

Results

Table 9. Log Scale Estimates for Crude and Adjusted Mixed Models Comparing Patients in Sites with and without Active Screening.

Parameter	Model 1: Crude Mean CD4 (P-Value)	Model 2: Adjusted Mean CD4 (P-Value)
Intercept	4.5923 (<0.0001)	4.5592 (<0.0001)
Active Screening (Active vs Non-Active)	0.01058 (0.91)	-0.03055 (0.76)
Site Patient- Provider Ratio		
(0-4.0 vs 8.6-11.99)	---	0.3000 (0.11)
(4.01-8.5 vs 8.6-11.99)	---	0.2251 (0.07)
(12-35.33 vs 8.6-11.99)	---	-0.02364 (0.84)
Site's ART Eligibility Criterion for Patients in WHO Clinical Stage 1 or 2 (<200 vs 200+ cells/μL)	---	-0.06920 (0.61)
Site's ART Eligibility Criterion for Patients in WHO Clinical Stage 3 (<350 vs 350+ cells/μL)	---	-0.02661 (0.84)

Table 10. Log Scale Estimates for Crude and Adjusted Mixed Models Comparing Patients in Sites with and without Active Screening Entry Points.

Parameter	Model 1: Crude Mean CD4 (P-Value)	Model 2: Adj. for Patient Factors Mean CD4 (P-Value)	Model 3: Adj. for Programmatic Factors Mean CD4 (P-Value)	Model 4: Adj. for Patient and Programmatic Factors Mean CD4 (P-Value)
Intercept	4.4418 (<0.0001)	4.5299 (<0.0001)	4.4648 (<0.0001)	4.5484 (<0.0001)
Active Screening Entry Points (Active vs. Non-Active)	0.2081 (0.03)	0.1911 (0.04)	0.2394 (0.004)	0.2244 (0.005)
Sex (Male vs Female)	---	-0.2351 (<0.0001)	---	-0.2349 (<0.0001)
Site Patient-Provider Ratio				
(0-4.0 vs 8.6-11.99)	---	---	0.1630 (0.23)	0.1470 (0.26)
(4.01-8.5 vs 8.6-11.99)	---	---	0.2016 (0.03)	0.2032 (0.03)
(12-35.33 vs 8.6-11.99)	---	---	-0.03376 (0.70)	-0.03158 (0.71)
Site's ART Eligibility Criterion for Patients in WHO Clinical Stage 1 or 2 (<200 vs 200+ cells/μL)	---	---	-0.1665 (0.11)	-0.1583 (0.12)

Sensitivity Analysis

Table 11. Median time to ART Initiation after Enrolling into Care for Active and non-Active Screening Sites.

	Active Screening Sites	Non-Active Screening Sites
Median time (days) to ART Initiation (IQR)	56 (21-140)	56 (19-167)

Table 12. Distribution of WHO Clinical Stage at ART Initiation, Sex and Age at ART Initiation for Patients With and Without CD4 Cell Count at ART Initiation.

	Patients With CD4 Cell Count N (%)	Patients Without CD4 Cell Count N (%)
WHO Stage at ART Initiation:		
Missing	679 (1.8)	332 (4.4)
I	5,909 (15.6)	1,233 (16.5)
II	8,005 (21.1)	1,420 (19.0)
III	17,335 (45.8)	3,108 (41.6)
IV	5,936 (15.7)	1,384 (18.5)
Males	13,607 (36.0)	2,586 (34.6)
Mean Age (years)	37.4	36.8

Table 13. Comparison of Study Results from the Active Screening Final Model with Results Based on Only Kenyan Sites.

Parameter	Final Model (Study Results) Mean CD4 (P-Value)	Final Model (Kenya Sites Only) Mean CD4 (P-Value)
Active Screening		
Yes	92.6 (0.76)	107.8 (0.30)
No	95.5 (ref)	118.0 (ref)
Site Patient Provider Ratio		
0-4.0	128.9 (0.11)	137.2 (0.51)
4.01-8.5	119.6 (0.07)	123.0 (0.77)
8.6-11.99	95.5 (ref)	118.8 (ref)
12-35.33	93.3 (0.83)	122.6 (0.75)
Site ART Eligibility Criteria for Patients in WHO Clinical Stage 1 or 2		
< 200 cells/μL	89.1 (0.61)	92.2 (0.25)
200+ cells/μL	95.5 (ref)	118.8 (ref)
Site ART Eligibility Criteria for Patients in WHO Clinical Stage 1 or 2		
< 350 cells/μL	93.0 (0.84)	No Estimates
350+ cells/μL	95.5 (ref)	Generated

Table 14. Comparison of Study Results from the Active Screening Entry Point Final Model with Results Based on Only Kenyan Sites.

Parameter	Final Model (Study Results) Mean CD4 (P-Value)	Final Model (Kenya Sites Only) Mean CD4 (P-Value)
Active Screening Entry Points		
Yes	118.2 (0.005)	138.0 (0.007)
No	94.5 (ref)	112.6 (ref)
Sex		
Male	74.7 (<0.0001)	85.9 (<0.0001)
Female	94.5 (ref)	112.6 (ref)
Site Patient Provider Ratio		
0-4.0	109.4 (0.26)	114.7 (0.92)
4.01-8.5	115.8 (0.03)	123.7 (0.28)
8.6-11.99	94.5 (ref)	112.6 (ref)
12-35.33	91.5 (0.71)	109.8 (0.72)
Site ART Eligibility Criteria for Patients in WHO Clinical Stage 1 or 2		
< 200 cells/μL	80.6 (0.12)	84.9 (0.13)
200+ cells/μL	94.5 (ref)	112.6 (ref)

Table 15. Comparison of Study Results from the Active Screening Final Model with Results Based on 1) Reclassification of "Partial" Sites as "Active Screening" and 2) Exclusion of "Partial" Sites.

Parameter	Final Model (Study Results) Mean CD4 (P-Value)	Final Model (Reclassification) Mean CD4 (P-Value)	Final Model (Exclusion) Mean CD4 (P-Value)
Active Screening			
Yes	92.6 (0.76)	97.50 (0.69)	99.5 (0.29)
No	95.5 (ref)	93.6 (ref)	90.0 (ref)
Site Patient Provider Ratio			
0-4.0	128.9 (0.11)	119.6 (0.19)	106.9 (0.29)
4.01-8.5	119.6 (0.07)	117.6 (0.06)	107.0 (0.14)
8.6-11.99	95.5 (ref)	93.6 (ref)	90.0 (ref)
12-35.33	93.3 (0.83)	88.2 (0.62)	84.3 (0.57)
Site ART Eligibility Criteria for Patients in WHO Clinical Stage 1 or 2			
< 200 cells/μL	89.1 (0.61)	87.1 (0.58)	79.6 (0.28)
200+ cells/μL	95.5 (ref)	93.6 (ref)	90.0 (ref)
Site ART Eligibility Criteria for Patients in WHO Clinical Stage 1 or 2			
< 350 cells/μL	93.0 (0.84)	92.9 (0.95)	96.7 (0.53)
350+ cells/μL	95.5 (ref)	93.6 (ref)	90.0 (ref)

Methodological Details: Chapter 4 (Active Screening Entry Points – Patient Survival)

Measures

Outcome variable:

For the purpose of our analysis, patients who were lost to follow-up where censored at the midpoint between their last recorded visit and the next scheduled visit.

Potential Confounders:

Patient-level Variables

Based on the results of assessment for linearity (see below for details), age at ART initiation was operationalized as a set of equally spaced indicator variables of five-year intervals ranging from age 18 to 88 years. Measures of socio-economic status (years of school completed, highest education level achieved, availability of electricity and piped water in the home, monthly income) could not be considered for statistical adjustment due to the high proportion of missing values.

Programmatic-level Variables

ART Eligibility Criteria

The sites' CD4 cell count criterion for ART initiation at each World Health Organization (WHO) stage was analyzed using a set of three indicator dichotomous variables: 1) for WHO clinical stages 1 and 2, sites using a CD4 count threshold of less than 200 cells/μL to initiate ART for patients with this clinical stage were compared with those using CD4 counts of 200 cells/μL or more; 2) for WHO clinical stage 3, sites using a CD4 count threshold of less than 350 cells/μL to initiate ART for patients with this clinical stage were compared with those using CD4 counts of 350 cells/μL or more; 3) for WHO clinical stage 4, sites using a CD4 count threshold

of less than 250 cells/μL to initiate ART for patients with this clinical stage were compared with those using CD4 counts of 250 cells/μL or more.

Patient-provider ratio

Patient-provider ratio was calculated for each site as the total number of patients on ART during the first quarter of 2008 divided by the total number of days providers are available. The first quarter of 2008 was chosen because it was the time closest to when 1) the provider information was collected and 2) all the sites had patients on ART. Note that the patient-provider ratio category of 12-35.53 was made considerably wider than the other three (ratios 0-4.0, 4.01-8.5, 8.6-11.99) to include the outlier value of 35.52; otherwise the range would have only extended to 18.54. Selection of the categories was based on the objective of dividing the sites into subgroups each with an equal number of sites of similar patient-provider ratios to minimize residual confounding [141].

*Fees for Services, ARV Stockouts, Frequency of CD4 Cell Monito*ring

Since there was virtually no variability in the responses, the following constructs were not considered for statistical adjustment: charging fees for services rendered (laboratory tests, first line ART, opportunistic infection prophylaxis, opportunistic infection treatment, routine follow-up care, and transportation to the clinic), experiencing ARV disruptions, frequency of CD4 cell count monitoring.

Site-level Variables

Site Classification

Sites were also classified as private or public. Due to a small number of private sites, this variable was not considered for statistical adjustment.

Statistical Analysis

Assessment of the Statistical Assumptions for Cox Proportional Hazards Models

The proportional hazards assumption was assessed twice: 1) separately for each variable included in the multivariable analysis and 2) while adjusting for other variables in the final model. Three different approaches were used: 1) log-log survival curves, 2) goodness of fit test, and 3) time-dependent covariates with different versions of time (e.g. survival time, heavyside function) in an extended Cox Proportional Hazards model [116]. Categorical variables were operationalized as such to produce log-log curves and as indicator variables when creating time-dependent covariates in extended Cox Proportional Hazards models. Selection of specific time points for heavyside functions were based on inspection of the log-log curves to identify time period(s) where the violations of the parallelism were evident [116]. When the proportional hazards assumption was assessed for the multivariable analysis, the respective means were used as the value for other variables in the model [116]. A variable was assumed to meet the proportional hazards assumption unless the log-log curves alone or both the goodness of fit test and the time-dependent assessment showed strong evidence of violation [116]**.** Except for the potential mediator, none of the variables tested show evidence of considerable violation of the proportional hazards assumption.

The linearity assumption for continuous variables patient-provide ratio and age at ART initiation was assessed separately for each variable using two approaches. We fitted a model with both a continuous and a squared-term version of the covariate and tested the statistical significance (using alpha = 0.05) of the squared-terms. Secondly, we fitted a bivariable Cox model of the outcome and covariate. Patient-provider ratio was modeled using three indicator variables for the four categories created for this variable (0-4.0, 4.01-8.5, 8.6-11.99 (reference

group), and 12-35.53), and age at ART initiation using eight indicator variables of five-year increments for the nine categories (18-23; 24-29; 30-35 (reference group)…66-88). The estimated beta estimates for the indicator variables were plotted and assessed for evidence of a linear pattern. Based on the results of these assessments, patient-provider ratio and age at ART initiation were operationalized using three and eight indicator variables, respectively.

Results

Sensitivity Analysis

Table 8. Key Statistics Used in Selecting the Final Active Screening Entry-Point (ASEP) Cox Proportional Hazards Model

Model	ASEP HR 95% CI (width)	Akaike Information Criterion
Standard	0.82 0.64-1.06 (0.42)	62995.12
Standard (Kenya Sites Only)	0.87 0.70-1.08 (0.38)	47285.52
Stratified Cox Model: Patient-Provider Ratio, g=4	0.82 0.64-1.06 (0.42)	57506.04
Stratified Cox Model: Site Type, g=3	0.83 0.64-1.06 (0.42)	56400.09

Table 9. Assessment of Mediation with Final Active Screening Entry Point Model (Model 5) Operationalizing CD4 Cell Count at ART Initiation (potential mediator) as a Continuous, Quartiles and Dichotomous Variable.

Model	ASEP Beta Estimate	Percent Change in Beta Estimate [(Crude-Adjusted/Crude)*100]
Final Active Screening Entry Point Model	-0.19605	Reference
Final Active Screening Entry Point Model Fitted With CD4 Cell Count at ART Initiation as:		
Continuous	-0.06916	64.7%
Quartiles	-0.06955	64.5%
Dichotomous	-0.19157	2.3%

Table 10. Proportion of Patients Lost to Follow-up or Recorded as Dead Within a Year Following ART Initiation Among Sites with Mainly Active and non-Active Screening Entry Points.

	Active Screening Entry Points N=24,725	non-Active Screening Entry Points N=20,616	OR (95% CI)
Number (%) of Patients Lost to Follow-up Within a Year of ART Initiation	4,755 (19.2%)	3,925 (19.0%)	1.0 (0.7-1.5)
Number (%) of Recorded Death Within a Year of ART Initiation	1,485 (6.0%)	984 (4.8%)	1.0 (0.6-1.8)

Table 11. Average Value of Last Recorded CD4 and of CD4 at ART Initiation for Patients Who Were Lost to Follow-up Within a Year After ART Initiation.

	Active Screening Entry Points N=4,755	non-Active Screening Entry Points N=3,925	P-Value
Mean CD4 Value Last Recorded CD4 (N (%))	112.8 cells/μL (4,219 (88.7%))	92.0 cells/μL (3,351(92.0%))	0.0451
Mean CD4 Value at ART Initiation (N (%))	84.0 cells/μL (3,925(82.5%))	73.2 cells/μL (3,048(77.7%))	0.06

Table 12. Results of Final Model Cox Model (Model 5) Assuming that all Patients Lost to Follow-Up, Within a Year of ART initiation, at Active Screening Entry Point Sites were Alive and Those From non-Active Screening Entry Point Sites Died.

Parameter	Model 5 (Final Model) HR (95% CI)
Active Screening Entry Points (Yes vs. No)	0.27 (0.24-0.29)
Sex (Male vs Female)	1.31 (1.25-1.37)
Sites by Type	
Health Center/Clinic vs District/Provincial Hospitals	0.90 (0.81-1.00)
Teaching/National Referral Hospital vs District/Provincial Hospitals	1.13 (0.99-1.30)
Site Patient-Provider Ratio	
0-4.0 vs 8.6-11.99	0.84 (0.64-1.10)
4.01-8.5 vs 8.6-11.99	0.98 (0.86-1.11)
12-35.33 vs 8.6-11.99	1.18 (1.05-1.32)
Patient Waiting List (Yes vs No)	1.31 (1.09-1.56)
Predominant Patient Population Served	
Rural vs Urban	0.76 (0.67-0.86)
In Between Urban/Rural vs Urban	0.77 (0.70-0.85)
Site's ART Eligibility Criterion for Patients in WHO Clinical Stage 1 or 2 (<200 vs 200+ cells/μL)	0.74 (0.62-0.89)

Table 13. Results of Final Model Cox Model (Model 5) Assuming that all Patients Lost to Follow-Up, Within a Year of ART initiation, at Active Screening Entry Point Sites Died and Those From non-Active Screening Entry Point Sites were Alive.

Parameter	Model 5 (Final Model) HR (95% CI)
Active Screening Entry Points (Yes vs. No)	3.25 (2.28-4.63)
Sex (Male vs Female)	1.22 (1.15-1.30)
Sites by Type	
Health Center/Clinic vs District/Provincial Hospitals	0.85 (0.69-1.04)
Teaching/National Referral Hospital vs District/Provincial Hospitals	1.40 (0.90-2.18)
Site Patient-Provider Ratio	
0-4.0 vs 8.6-11.99	1.42 (0.71-2.83)
4.01-8.5 vs 8.6-11.99	0.96 (0.67-1.36)
12-35.33 vs 8.6-11.99	1.02 (0.88-1.19)
Patient Waiting List (Yes vs No)	3.05 (2.42-3.84)
Predominant Patient Population Served	
Rural vs Urban	1.23 (0.84-1.80)
In Between Urban/Rural vs Urban	0.99 (0.86-1.15)
Site's ART Eligibility Criterion for Patients in WHO Clinical Stage 1 or 2 (<200 vs 200+ cells/μL)	0.35 (0.25-0.50)

Appendix B

IeDEA Site Assessment Tool

IeDEA East Africa Brief Follow-up Questionnaire

IeDEA
International epidemiologic Databases to Evaluate AIDS

Site Name*_____

Address: _____
street

_____
city/district state/province postal code

_____
country

If the care and treatment program at this facility part of a larger network (e.g., AMPATH, MTCT-Plus, FACES, etc), please list the network name here: _____

	Name	Contact Number	Email
Primary contact			
Data manager			

A. SITE CHARACTERISTICS The term "site" is used to refer to the larger institution (i.e. hospital, health center) where the HIV care and treatment "facility" is located.

No.	QUESTIONS AND INSTRUCTIONS	RESPONSES		SKIPS
A01	Please indicate the availability of the internet for the **support** staff who work at the clinic (0% = no availability any time whereas 100% = continuous access at any time. At this facility, internet is open and available on site to **support** staff about _____% of the time. (**Support staff** would include data base and study manager and/or persons in clerical or administrative positions or lay or outreach workers.)			
A02	Please indicate the availability of the internet for the **clinical** staff who work at the clinic (0% = no availability any time whereas 100% = continuous access at any time. At this facility, internet is open and available to **clinical** staff about _____% of the time. (**Clinical staff** would include nurses, clinical officers, physicians, physicians assistants, pharmacists, etc.)			
A03	Do you maintain an electronic database at your site? *Please circle the number (s) corresponding to all applicable responses.*	YES, site has an electronic medical record and data are stored on a computer. YES, we use paper for recording patient notes but transfer information to an electronic database stored in a computer at our site. No, we complete patient information on paper forms and then transfer the forms to a data center for centralized data entry and storage. NO Other (specify)_____	1 2 3 4 5	
A04	Is the patient population served by your clinic… *Please circle the number (s) corresponding to all responses that apply.*	Urban-city (officially designated to be city with city administration and political bodies) Urban-other (big and small towns, peri-urban areas, growth points, mining communities) Rural-communal (subsistence farming areas) Rural-other (large and small scale commercial farming areas) In-between urban/rural such as a small town, peri-urban area, growth points, mining community, etc.	1 2 3 4 5	

No.	QUESTIONS AND INSTRUCTIONS	RESPONSES		SKIPS
A05	What patients do you see? *Please circle the number (s) corresponding to all applicable responses.*	Adults only Children only Adults and children in separate clinics Adults and children in combined or family clinics	1 2 3 4	

A06	**LEVEL OF CARE AVAILABLE TO HIV PATIENTS AT YOUR HIV CARE SITE.** **Please complete table. If not applicable, please enter the number 0**	Type of Clinic Check (√) the response that best describes your clinic.		Approximate Number of adult HIV+ patients Daily census HIV+ (on HIV clinic days)	Approximate Number of child HIV+ patients Daily census HIV+
		Public or Government	Private Clinic	HIV+ Adults Daily	HIV+ Children Daily
	Primary (health center/clinic)				
	Secondary (district/provincial hospital)				
	Tertiary (teaching/national referral hospital)				

A07	Is an Intensive Care Unit available at the facility? *Please circle the number (s) corresponding to all applicable responses.*	On site Off site Not available	1 2 3	
A08	How many inpatient beds (approximately) are there at this site/facility? *Please write-in a number on the blank.*	_____ Beds		
A09	How many exam/consultation rooms are there in the HIV care and treatment facility/clinic? *Please write-in a number on the blank.*	_____ exam rooms		
A10	What is the highest level of care available for referral of very sick patients at the facility? *Please circle the number (s) corresponding to all applicable responses.*	Hospital with sub-specialists (cardiologist, pulmonologist, etc.) District hospital with medical officer or general specialist Not applicable	1 2 3	

A11. STAFFING CHARACTERISTICS AND STAFF TURNOVER

No.	QUESTIONS AND INSTRUCTIONS	RESPONSES	SKIPS

How many of the following staff at this site are currently caring for or working with persons with HIV? Please enter "0" if not applicable

Physicians: Only includes medical doctors.
Mid-level providers (clinical officers, nurse practitioners, physicians assistants, not nurses)
Nurses: Nurses working in clinical care.
Lay health worker: Individual with no professional clinical training (e.g. counselor)

	Sun	Mon	Tues	Wed	Thurs	Fri	Sat
Physicians (other than pediatricians)							
Pediatricians							
Mid level providers							
Nurses/Midwives							
Nursing assistants							
Lay health workers or Adherence counselors or Outreach workers							
Pharmacists							
Pharmacy assistants							
Nutritionists							
Data capturers							

ADULT CARE AND TREATMENT QUESTIONS BEGIN HERE

ADULT CARE AND TREATMENT QUESTIONS

No.	QUESTIONS AND INSTRUCTIONS	RESPONSES	SKIPS
A12	When did the facility begin providing HIV care for adults?	*Please use the date format yyyy for YEAR* ☐☐☐☐	
A13	When did the facility begin providing ART for adults?	*Please use the date format yyyy for YEAR* ☐☐☐☐	
A14	Please indicate clinic days for adult patients followed at this facility. ***If this facility serves only pediatrics, indicate NA (NOT APPLICABLE) here and complete pediatric module.*** ***If this facility serves families, please complete both the adult and pediatric modules of this assessment.***	 For example, if the clinic is open to patients on Monday, Tuesday, and Wednesday mornings and afternoons and Friday morning, indicate as follows:	NA

	Sun	M	T	W	Th	F	Sa
AM							
PM							

	Sun	M	T	W	Th	F	Sa
AM		x	x	x		x	
PM		x	x	x			

A15	Please rank the most common points of entry into this care and treatment program for adult patients from most common to least common, with 1 being the most common and 10 being the least common. *Enter a '1' next to the primary point of entry for patients at the care and treatment facility. Enter a '2' next to the point of entry for the care and treatment facility from which the second highest proportion of patients originate. Etc. For example, if about 70% of patients come through VCT and 30% of patients through PMTCT then you would enter a "1" next to VCT and a "2" next to PMTCT.* *If patients do not enroll into the care and treatment program through a given point of entry at the right leave it blank.*	*Circle the number corresponding with any point of entry.* Provider Initiated Testing and Counseling_____ 1 PMTCT within the ANC _____ 2 VCT directly _____ 3 VCT via referral (e.g., as a family, household member, or sex partner of an index patient already enrolled at the site)_____ 4 PMTCT in labor and delivery/maternity____ 5 In-patient wards_____ 6 Outpatient ward_____ 7 TB clinic_____ 8 STI clinic _____ 9 Treatment failure elsewhere ____ 10 Other medical referral ____ 11 Other_____ 12 (Please specify Other)

A16	Do you record a national ID or government ID in your database or on patient records? *(Circle the number of the correct response.)*		YES NO	1 2	
A17	Do you create a unique identifier for every patient in your clinic site? *(Circle the number of the correct response.)*		YES NO	1 2	
A18	Is it possible to link a patient's records to… *(Circle the number of the correct response to each.)*	…a spouse or partner's records?	YES NO	1 2	
A18b	Is it possible to link a patient's records to… *(Circle the number of the correct response to each.)*	….a child's records?	YES NO	1 2	
A19	Do you identify patients who were transferred in? *(Circle the number(s) of the correct response.)*		YES, In electronic database YES, In charts or patient records NO Not applicable/Other _____ (Please specify Other)	1 2 3 4	
A20	Are transfers out of the clinic recorded in the database? *(Circle the number of the correct response.)*		YES NO Not applicable	1 2 3	
A21	After a patient was transferred out do you get any information on the patient (eg: vital status)? *(Circle the number of the correct response.)*		YES NO Not applicable	1 2 3	
A22	For your female patients, do you record history of PMTCT? *(Circle the number of the correct response.)*		YES, In electronic database YES, In charts or patient records No Not applicable/Other	1 2 3 4	
A23	For an individual patient, do you record…. *(Circle the correct response to each.)*	Education level Socio-economic status (Income, employment, etc.)	YES YES	NO NO	
A24	Do you record if a patient has health insurance? *(Circle the number of the correct response.)*		YES NO	1 2	
A25	What percentage of your patients have health insurance? *(Please specify percentage in blank provided.)*		_____% **If unknown, circle NA, If none have health insurance, put "0"**		

A26	Do patients pay for costs of following care & services? (*check all that apply*) a. Screening consult: ☐ No (free) ☐ Yes – full pay ☐ Yes – partial pay ☐ depends on insurance ☐ unknown b. Laboratory tests: ☐ No (free) ☐ Yes – full pay ☐ Yes – partial pay ☐ depends on insurance ☐ unknown c. Diagnostic exams: ☐ No (free) ☐ Yes – full pay ☐ Yes – partial pay ☐ depends on insurance ☐ unknown d. 1st-line ART: ☐ No (free) ☐ Yes – full pay ☐ Yes – partial pay ☐ depends on insurance ☐ unknown e. 2nd-line ART: ☐ No (free) ☐ Yes – full pay ☐ Yes – partial pay ☐ depends on insurance ☐ unknown f. OI prophylaxis ☐ No (free) ☐ Yes – full pay ☐ Yes – partial pay ☐ depends on insurance ☐ unknown g. OI treatment ☐ No (free) ☐ Yes – full pay ☐ Yes – partial pay ☐ depends on insurance ☐ unknown h. Routine follow-up consult: ☐ No (free) ☐ Yes – full pay ☐ Yes – partial pay ☐ depends on insurance ☐ unknown i. Additional consults: ☐ No (free) ☐ Yes – full pay ☐ Yes – partial pay ☐ depends on insurance ☐ unknown j. Travel to clinic: ☐ No (free) ☐ Yes – full pay ☐ Yes – partial pay ☐ depends on insurance ☐ unknown k. Viral Load tests ☐ No (free) ☐ Yes – full pay ☐ Yes – partial pay ☐ depends on insurance ☐ unknown	
A27	The following questions pertain to the promotion and conduct of HIV testing among relatives, sex partners, and other household members of the patients receiving care(pre-ART/ART) at this facility and for whom HIV status may be unknown. **Which of these best describes current practices?**	
A27a	HIV testing is routinely **recommended** by providers for relatives, sex partners, and other household members of the patients enrolled in HIV care at this facility.	*Please check the best answer(s)* YES NO Don't Know *Relatives* ☐ ☐ ☐ *Sex partners* ☐ ☐ ☐ *Other household adults* ☐ ☐ ☐ *Children in or around the household.* ☐ ☐ ☐
A27b	HIV testing is routinely **made available** to relatives, sex partners, and other household members of the patients enrolled in HIV care at this facility.	*Please check the best answer(s)* YES NO Don't Know *Relatives* ☐ ☐ ☐ *Sex partners* ☐ ☐ ☐ *Other household adults* ☐ ☐ ☐ *Children in or around the household.* ☐ ☐ ☐
A27c.	If available, please specify the year in which HIV testing of relatives, sex partners, and other household members began at this facility.	_____(YYYY)
A28	Which of the following best describes the current approach(es) to **HIV care and treatment** at this facility?	

A28a	HIV/AIDS <u>care and treatment</u> are actively extended to the HIV positive family, household members, and sex partners of the patient enrolled in care and treatment at this facility.	*Please check the best answer(s)* *Relatives* ☐ YES ☐ NO ☐ *Don't Know* *Sex partners* ☐ ☐ ☐ *Other household adults* ☐ ☐ ☐ *Children in or around the household.* ☐ ☐ ☐		
A28b	If available, please specify the year in which HIV/AIDS care and treatment for extended family, household, and partners began at this facility.	_____(YYYY)		

B. PROGRAM CHARACTERISTICS Program characteristics refer to the characteristics of the services provided to patients at this HIV care and treatment facility. This includes clinical and other services such as laboratory, outreach, and adherence support, **as well as linkage between pharmacy and patient records, and antiretroviral (ARV) and other drug supply.**

No.	QUESTIONS AND INSTRUCTIONS	RESPONSES		SKIPS
B01	How is malaria diagnosed at this facility? *Circle the number(s) of the correct response(s).*	Presumptive diagnosis Thick smear Rapid Test Other *(specify)*_____ Not applicable (malaria not assessed at this facility)	1 2 3 4 5	
B01b	Do you capture malaria diagnoses in your clinical database?	*Please circle the number of the best response.* YES NO Other _____	1 2 3	
B02	Which patients followed at this facility receive free bed nets? *Please circle the number (s) corresponding to all applicable responses.*	Bed nets are not distributed to patients at this facility All patients All pediatric patients All pediatric patients <5 years All pregnant women All patients diagnosed with malaria Other (specify)_____ Not applicable	1 2 3 4 5 6 7 8	
B03	Please indicate which PMTCT programs or services are available on-site. *Please circle the number(s) for all applicable responses.*	ANC PMTCT within the ANC Labor & delivery (L&D) PMTCT within L&D Other (specify)_____ None	1 2 3 4 5 6	

No.	QUESTIONS AND INSTRUCTIONS	RESPONSES		SKIPS
B04	Please indicate which prevention and other clinical services are available on-site. *Please circle the number(s) for all applicable responses.*	HIV counseling and testing Counseling regarding disclosure to sexual partners Education on sexual behavior changes and safer sex methods Provision of condoms Family planning for prevention of mother to child transmission (aside from condoms) Referral for on-site screening for sexually transmitted infections (STIs) Education on high-risk substance-use behaviors and harm reduction practices Screening for drug and alcohol abuse and when appropriate, referring for substance abuse treatment Post-exposure prophylaxis (PEP) Male circumcision for infants Male circumcision for adults TB screening TB treatment Other (specify)_____ None of the above	1 2 3 4 5 6 7 8 9 10 11 12 13 14	
B05	Please indicate which support services are available for persons followed by this facility. *Please circle the number(s) for all applicable responses.*	Support groups for HIV+ persons Peer educator program available to patients Outreach program for patients who miss appointments Pre-ART outreach Program Other (specify)_____ None	1 2 3 4 5 6	

B06	What ART adherence support activities are provided for patients followed at this facility? *Please circle the number(s) for all applicable responses.*	One-on-one counseling Group counseling Appointment slips Written/pictorial patient education material Pill boxes or blister packs Calendars, checklists, or other reminders Educational videotapes Alarm clocks, wrist watches, beepers Pharmacist included on multidisciplinary team Routine review of medication pick up No ART adherence activities are provided Other (specify)_____ None	1 2 3 4 5 6 7 8 9 10 11 12 13	
B07	How often are patients counseled about ART adherence? *Please circle the number of the answer that best applies*	At ART initiation only At ART initiation and more than once a month thereafter At ART initiation and once every 1-3 months thereafter At ART initiation and once every 4-6 months thereafter At ART initiation and infrequently thereafter Less frequently Frequency is based on suspected viral failure Other (specify)_____ Not Applicable	1 2 3 4 5 6 7 8 9	
B08	How often do adult patients actually receive a anthropometric or weight for height evaluation in this facility? *Please circle the number of the answer that best applies*	Only at enrolment Once a month Once every 3 months Once every 6 months Other (specify)_____ Not done	1 2 3 4 5 6	
B09	What specific nutritional support services are being provided to adult patients at this facility? *Please circle the number(s) for all applicable responses.*	Nutritional counseling Multivitamins without minerals supplementation Multivitamins & minerals supplementation Vitamin A supplementation for women postpartum Vitamin A given to other adults Iron supplementation Zinc Nutritional 'treatment' for severely malnourished adults Food rations Food rations to promote ART adherence (i.e., incentive program) Food rations to promote household food security (i.e., supplementary feeding program) Agricultural Support (training, materials) Income generating activities for PLWHAs Other(specify)_____ None	1 2 3 4 5 6 7 8 9 10 11 12 13 14 15	

B. PROGRAM CHARACTERISTICS Program characteristics refer to the characteristics of the services provided to patients at this HIV care and treatment facility. This includes clinical and other services such as laboratory, outreach, and adherence support, as well as linkage between pharmacy and patient records, and antiretroviral (ARV) and other drug supply.

No.	QUESTIONS AND INSTRUCTIONS	RESPONSES		SKIPS
B10	Do you provide nutritional support services to…? *Please circle the number of all responses that apply.*	All HIV patients Only when clinically indicated Special subgroup of patients (eg: Children/On ART/Pregnant women) Persons with severe malnutrition Persons with metabolic disorders (dislypidemia, overweight, diabetes) other (specify) _____ None	1 2 3 4 5 6	
B11	What is the recommended frequency of CD4 testing for adult patients who are pre-ART followed at this facility? *Please circle the number of the answer that best applies*	Baseline only Once every 6 months Once every 12 months Less frequently Varies by caregiver Not done Other (describe below)_____ _____ _____	1 2 3 4 5 6 7	
B12	What is the recommended frequency of viral load testing for adult patients who are pre-ART followed at this facility? *Please circle the number of the answer that best applies*	Baseline only Once every 6 months Once every 12 months Less frequently Only when clinically indicated Varies by caregiver Other _____ Not done	1 2 3 4 5 6 7 8	
B13	Is clinical and laboratory information for pre-ART monitoring and care visits captured in the chart of patients followed at this facility?	*Please circle the number of the best response.* YES NO	1 2	
B14	Is clinical and laboratory information on the pre-ART monitoring and care visits captured in the patient-level database that is maintained at this facility?	*Please circle the number of the best response.* YES NO	1 2	

No.	QUESTIONS AND INSTRUCTIONS	RESPONSES		SKIPS
	Questions BELOW refer to PRE-ART and ART initiation in adult patients .			
B15	When is cotrimoxazole prophylaxis prescribed for adult patients followed at this facility? *Please circle the number(s) of all applicable responses.*	CD4 < 500 CD4 < 350 CD4 < 200 WHO stage 3 or 4 Not prescribed at all for adult patients Other (specify)_____ Varies by caregiver	1 2 3 4 5 6 7	
B16	Do you have a waiting list for initiating ART for adult patients followed at this facility? *Please circle the number of the best response.*	YES NO Not Applicable	1 2 3	
B17	What determines the rank on the waiting list for adult patients followed at this facility **when you are not able to treat all eligible patients?** *Please circle the number(s) of the best responses.*	CD4 count WHO stage Attendance at adherence counseling sessions Adherence to pre-ART care Other (specify)_____ Not applicable	1 2 3 4 5 6	
B18	What staging system is used in your cohort? *Please circle the number of the best response.*	CDC WHO Other (specify)_____ None	1 2 3 4	
B19	What CD4 criteria are used for ART initiation at each WHO stage? *If WHO stage is not used, please circle Not Applicable.*	(enter CD4 threshold) WHO 1 _____ WHO 2 _____ WHO 3 _____ WHO 4 _____ Not Applicable		
B20	Do you use HIV Viral Load as a criteria to determine when to start ART? *Please circle the number of the best response.*	YES NO Not Applicable	1 2 3	
B21	If HIV VL is used, what is the threshold above which you treat regardless of CD4 count?	_____ Copies per mL		

B22	If the decision to start antiretroviral therapy for adult patients is based on criteria in addition to CD4 cell count or stage of HIV disease, please indicate which criteria are used. *Please circle the number(s) of all applicable responses.*	Ability to pay Availability of treatments Adherence to treatment Psychosocial criteria (buddy/disclosure) Residence in catchment area Pregnancy Rank on the waiting list Disclosure of HIV status Delay of ART due to co-morbid conditions (e.g. TB) Other(specify)_____ None of the above	1 2 3 4 5 6 7 8 9 10 11	
	Questions BELOW refer to adult patients who miss clinic visits			
No.	**QUESTIONS AND INSTRUCTIONS**	**RESPONSES**		**SKIPS**
B23	What do you do if an adult patient misses a visit? *Please circle the number(s) of all that apply*	Send a letter Telephone call Home visit by clinic staff Home visit by outreach workers (lay staff) Check hospital records Check pharmacy records Only visit a sample of all missed patients Other (specify) _____	1 2 3 4 5 6 7 8	
B23b	How soon after the missed visit are these procedures implemented? *Please specify time such as 60 days after last visit OR specify number of visits missed before outreach is begun – whichever is applicable to your facility.*	*Please specify time such as 60 days after last visit OR specify number of visits missed before outreach is begun.* _____ (time: specify number of days or months) OR _____ (number of missed visits)		
B24	How do you currently define "lost to follow-up" in adult pre-ART patients followed at this facility? *Please circle the number of the best response.*	No contact with facility >3 months No contact with facility >6 months No contact with facility >12 months Other	1 2 3 4	
B25	How do you currently define "lost to follow-up" in adult ART patients followed at this facility? *Please circle the number of the best response.*	No contact with facility >1 month No contact with facility >3 months No contact with facility >6 months No contact with facility >12 months Other	1 2 3 4 5	
B26	What, in your opinion, is the major cause of adult patients being lost to follow-up? *Please circle the number(s) of all applicable responses.*	Unascertained death Family lack of financial resources Lack of disclosure to family or neighbors Transfers out / Relocations Other(specify)_____	1 2 3 4 5	

B27	How do you ascertain deaths of adult patients in your clinic? *Please circle the number(s) of all applicable responses.*	Active outreach Family Word of mouth Physician report Data linkage with records at the site Phone follow-up Home follow-up (specify)_____	1 2 3 4 5 6 7 8	
B28	Do you document date of death, if known?	YES NO Comment_____	1 2	
B29	Do you document cause of death, if known?	YES NO Comment_____	1 2	

Questions BELOW refer to recording OI events and malignancies <u>at this facility</u>

No.	QUESTIONS AND INSTRUCTIONS	RESPONSES		SKIPS
B30	Is the history of OIs documented at first visit? *Please circle the number of the best response.*	YES, In charts or patient records YES, In electronic database NO Not applicable/Other _____	1 2 3 4	
B31	Are OI's recorded? *Please circle the number of the best response.*	At initial diagnosis At each visit until resolved Not routinely documented	1 2 3	
B32	Is the occurrence of malignancies recorded? *Please circle the number of the best response.*	YES, on paper YES, in the database Not routinely captured	1 2 3	
B33	Is the occurrence of malignancies reported to a registry? *Please circle the number of the best response.*	YES NO	1 2	

Questions BELOW refer to availability laboratory services.

B34	What is the availability and location of laboratory testing for patients followed at this facility? *(Please complete table below. Check or write in the appropriate responses)*		

	Test	Availability			Turn-around Time (estimate)	Disruption in reagents in last year		Data Available in...		
	Laboratory Test	On Site	Off Site	Test Not Available	Number of DAYS	YES	NO	CHART	Electronic medical record	Not Available
	HIV RNA PCR:	☐	☐	☐ NA	_____	☐ Yes	☐ No	☐ chart	☐ EMRS	☐ NA
	HIV DNA PCR	☐	☐	☐ NA	_____	☐ Yes	☐ No	☐ chart	☐ EMRS	☐ NA
	CD4 count	☐	☐	☐ NA	_____	☐ Yes	☐ No	☐ chart	☐ EMRS	☐ NA
	Hemoglobin	☐	☐	☐ NA	_____	☐ Yes	☐ No	☐ chart	☐ EMRS	☐ NA
	Total lymphs	☐	☐	☐ NA	_____	☐ Yes	☐ No	☐ chart	☐ EMRS	☐ NA
	ALT/AST	☐	☐	☐ NA	_____	☐ Yes	☐ No	☐ chart	☐ EMRS	☐ NA
	Cholesterol	☐	☐	☐ NA	_____	☐ Yes	☐ No	☐ chart	☐ EMRS	☐ NA
	Creatinine	☐	☐	☐ NA	_____	☐ Yes	☐ No	☐ chart	☐ EMRS	☐ NA
	Lactate	☐	☐	☐ NA	_____	☐ Yes	☐ No	☐ chart	☐ EMRS	☐ NA

B35	Does a specimen bank/repository (i.e., -70C freezer) exist at this facility for long-term storage of specimens for later testing as part of research studies? *Please circle the number of the best response.*	YES NO Comment: _____	1 2	
B36	Which of the following assays are used for CD4 tests? *Please circle the number(s) of all applicable responses.*	Flow cytometry Fascan FACSCalibur Truecount Calculation based on WBC and/or TLC	1 2 3 4 5	
B37	HIV viral load assay (s)... *Please circle the number(s) of all applicable responses – circle all responses that apply.*	P24 bDNA Nucleisens Biomerieux (ex-NASBA) Roche Amplicor Other Not available	1 2 3 4 5 6	
B38	What is the current lower limit of detection of HIV RNA assay? *Please circle the number of the best response.*	<500 copies/ml <400 copies/ml <50 copies/ml <20 copies/ml <10 copies/ml Other Do not know Not applicable	1 2 3 4 5 6 7 8	

Questions BELOW refer to the linkage between pharmacy and patient records

No.	QUESTIONS AND INSTRUCTIONS	RESPONSES		SKIPS
B39	Does the pharmacy that dispenses ART medications reside within HIV care and treatment facility? *Please circle the number of the best response.*	YES No, but it is on-site within the larger hospital NO, it is off-site Comment_____	1 2 3	

No.	QUESTIONS AND INSTRUCTIONS	RESPONSES		SKIPS
B40	Is there an electronic database in your pharmacy that tracks distribution of ART at the patient-level? *Please circle the number of the best response.*	YES NO	1 2	
B41	Does the pharmacy database also track the distribution of other medications such as **cotrimoxazole?** *Please circle the number of the best response.*	YES NO There is no pharmacy database	1 2 3	
B42	Can a patient's records in the pharmacy database be linked to the patient's records in the patient database at the care and treatment facility using a common patient identifier? *Please circle the number of the best response.*	YES No Perhaps, with a little work Perhaps, with a lot of work Don't know There is no pharmacy database Other (specify)_____ Not applicable	1 2 3 4 5 6 7 8	
	Questions BELOW refer to ARV drug availability and disruptions in ARV and other drug supply			
No.	**QUESTIONS AND INSTRUCTIONS**	**RESPONSES**		**SKIPS**
B43	What types of medications are available for <u>first line</u> ARV regimens of patients at this facility? *Please circle the number(s) for all applicable responses.*	WHO/UNAIDS regimen US FDA-approved US FDA tentatively approved Other (specify)_____ We have access to all available drugs	1 2 3 4 5	
B44	How is antiretroviral use recorded? *Please circle the number(s) of the best responses.*	Start date End date Current therapy at visit Other (specify)_____ Not recorded	1 2 3 4 5	
B45	How do you measure or assess adherence to ART for adult patients followed at this facility? *Please circle the number for all applicable responses.*	Do not routinely measure adherence Frequency of clinic visits Drugs taken in last week, day, months, etc. Pill count Viral load Pharmacy record Asking patient about adherence in past 3 days Answering the questions "Have you missed any...?" (i.e., self-report) Other (specify)_____	1 2 3 4 5 6 7 8 9	

	Questions BELOW refer to ARV drug availability and disruptions in ARV and other drug supply			
No.	QUESTIONS AND INSTRUCTIONS	RESPONSES		SKIPS
B46	What is the period covered by the first prescription of ARV (i.e., for patients starting ARV for the first time in this clinic)? *Please circle the number of the best response or provide alternative comments.*	15 days 30 days 31-60 days 61-90 days Other(specify)_____ _____ _____ _____	1 2 3 4 5	
B47	What is the period covered by subsequent ARV prescriptions once the patient is considered stable? *Please circle the number of the best response.*	30 days 31-60 days 61-90 days 6 months Other(specify)_____ _____ _____ _____	1 2 3 4 5	
B48	Does the facility document stock-out? *Please circle the number of the best response.*	YES No Do not know Not Applicable	1 2 3 4	
B49	In the past year, were there any disruptions of ARV drug supply such that some patients (new or existing) who needed ARV therapy did not receive it? *Please circle the number of the best response.*	YES No Do not know Not Applicable	1 2 3 4	
B50	How long was the worst disruption in ARV drug supply in the last 6 months? *Please circle the number of the best response.*	1 day only 2-7 days 8-21 days > 21 days Other (specify)_____ Unknown Not applicable	1 2 3 4 5 6 7	
B51	In the previous year, did you have any prophylactic or OI drug supply disruptions? *Please circle the number of the best response.*	YES No Do not know Not Applicable	1 2 3 4	

Questions BELOW refer to adverse events monitoring/pharmacovigilance at this facility

No.	QUESTIONS AND INSTRUCTIONS	RESPONSES		SKIPS
B52	**Are adverse events routinely documented in the patient charts?** *Please circle the number of the best response.*	**YES, almost universally** **YES, but with variable consistency** **Usually not** Other(specify)_____ **Not applicable**	**1** **2** **3** **4** **5**	
B53	**Are ARV-related adverse events routinely recorded in the database?** *Please circle the number of the best response.*	**No** **YES, as free text** **YES, coded** **YES, but only as a reason for treatment interruption**	**1** **2** **3** **4**	
B54	Are the outcomes of adverse events recorded? *Outcome could mean death, hospitalization, treatment change, or other* *Please circle the number(s) of the applicable responses.*	No YES, on paper only YES, in database as free text YES, in database, coded YES by virtue of their being the reason for treatment interruption YES by virtue of their being a cause of death and/or hospitalization No database available	1 2 3 4 5 6 7	
B55	Is pregnancy routinely documented in women treated with antiretroviral drugs? *Please circle the number of the best response.*	YES, on paper YES, in the database Not routinely captured	1 2 3	
B56	Are birth outcomes recorded for infants exposed to antiretroviral drugs *in utero*? *Please circle the number of the best response.*	YES, on paper YES, in the database Not routinely captured	1 2 3	
B57	For the major treatment-related adverse events listed, please specify whether a **standard case definition** is used.			

Major adverse events	Standardized case definition? YES	NO	Other DEFINITION
IRS			
Rash			
Peripheral neuropathy			
Hepatoxicity			
Other			

B58	What classification system is used for defining and grading HIV treatment-related adverse events? *Please circle the number of the best response.*	DAIDS toxicity grading scheme ACTG/HPTN Appendix 60 IMPAACT Appendix 40 WHO ANRS TAHOD specifications Clinical experience Other(specify)_____	1 2 3 4 5 6 7 8	

Questions BELOW REFER TO PMTCT SERVICES				
No.	QUESTIONS AND INSTRUCTIONS	RESPONSES	SKIPS	
B59	What is the relationship with the PMTCT programs associated with this HIV care and treatment program? *Please circle the number(s) for all applicable responses.*	There is no PMTCT program associated with this facility PMTCT is embedded in care and treatment program Programs are both on-site and linked PMTCT program is off-site and linked to care and treatment program PMTCT program is off-site and not linked to care and treatment program	1 2 3 4 5	
B60	What is the availability of infant diagnostic testing for patients followed at this facility? *Please circle the number of the best response.*	Available on-site Available off-site Not available at all	1 2 3	
B61	What type of infant diagnostic testing is used? *Please circle the number(s) for all applicable responses.*	DNA RNA Unsure Not done at this site	1 2 3 4	
B61	How do you typically diagnose pediatric HIV infection in patients over 18 months of age? *Please circle the number(s) for all applicable responses.*	Clinical criteria/IMCI algorithm 1 rapid test 2 rapid tests 1 ELISA 2 ELISA Western Blot Not Applicable/not done at this site Other	1 2 3 4 5 6 7 8	
Questions BELOW REFER TO ORAL DIAGNOSIS of LESIONS				
No.	QUESTIONS AND INSTRUCTIONS	RESPONSES	SKIPS	
B62	Do you examine the oral cavity for HIV-related lesions or disease conditions? *Please circle the number of the best response.*	YES, we ***examine*** the oral cavity for HIV-related lesions and diseases. NO, we do not examine the oral cavity.	1 2	

B63	Do you ever record a diagnosis of any of the following ORAL or OROPHARYNGEAL lesions or disease conditions? *(Please either YES, NO, or DK – don't know)*	Candidiasis: • Pseudomembranous Candidiasis (Thrush) • Erythematous Candidiasis • Angular Cheilitis • Hyperplastic Candidiasis	YES YES YES YES	NO NO NO NO	DK DK DK DK
		Histoplasmosis: • Mucosal surface ulcerations	YES	NO	DK
		Cryptococcus Neoformans : • Hard palate ulcerations	YES	NO	DK
		Herpes Simplex: • Primary herpetic gingivostomatitis • Recurrent oral Herpetic lesions	YES YES	NO NO	DK DK
		Herpes Zoster: • Multiple vesicular lesions on the facial skin, lips and oral mucosa	YES	NO	DK
		Human Papillomavirus: • Oral warts	YES	NO	DK
		Cytomegalovirus: • Oral necrotic ulcers with a white halo	YES	NO	DK
		Epstein-Barr Virus (EBV): • Oral hairy leukoplakia	YES	NO	DK
		Periodontal Disease: • Linear gingival erythema • Necrotizing ulcerative periodontitis • Palatal and gingival granulomatous masses in the oral cavity	YES YES YES	NO NO NO	DK DK DK
		Kaposi's Saracoma : • Red, blue, or purplish intraoral / oropharynx lesions	YES	NO	DK

TUBERCULOSIS SECTION

C.-Tuberculosis. FACILITY CHARACTERISTICS RELATED TO TUBERCULOSIS CARE Please answer this section only if the facility treats patients with tuberculosis. The term facility is used to refer to the clinic or service (i.e. care and treatment clinic) in a larger institution. The term "facility" is to be distinguished from "site" (which refers to the larger institution in which the care and treatment facility resides).

No.	QUESTIONS AND INSTRUCTIONS	RESPONSES		SKIPS
C01	Is TB diagnosed and treated by clinicians within the ARV program? *Please circle the number of the best response.*	Yes, at ART initiation only Yes, at ART initiation and regularly thereafter No, symptomatic patients are referred to the TB clinic	1 2 3	
C02	For HIV patients at this facility with TB, who treats their TB? *Please circle the number of the best response.*	HIV care and treatment facility TB clinic on-site TB clinic off-site Other (specify)_____	1 2 3 4	

HOW DO YOU SCREEN FOR TB?

C03	*(select the best response for each question below by placing a check(√) in the appropriate column)*	**YES, for everyone screened for TB**	**YES, but only if symptomatic or have a history of contact with a TB case**	**NO**
C04	Do you ask about symptoms as part of standard history during consultation?			
C05	Do you have a formal questionnaire based on symptoms and signs?			
C06	Do you administer a Tuberculin skin test (TST)?			

C07	Are chest X-rays…? *Please circle the number(s) of the appropriate responses.*	Available on-site Available off-site Not available For all TB patients For some TB patients Not at all	1 2 3 4 5	
C08	Do patients have to pay for chest X-rays? *Please circle the number of the best response.*	Yes No Unknown Paid by insurance or other medical coverage	1 2 3 4	
C09	Is isoniazid (INH) prophylaxis available for? *Please circle the number(s) of the most appropriate responses.*	For all patients For all TST+ For TST+ contacts of a TB case For all contacts TST+ or TST(-) Other_____ Not available at this site	1 2 3 4 5 6	
C10	Are sputum smears for AFB…? *Please circle the number of the best response.*	Yes, available for everyone Yes, available only if symptomatic No	1 2 3	

No.	QUESTIONS AND INSTRUCTIONS		RESPONSES		SKIPS
C11	Is sputum cultured for TB? *Please circle the number(s) of the best responses.*		Routinely available for everyone Available for smear-positive cases Available for smear negative cases Available for treatment failures, relapses and MDR suspects Not available	1 2 3 4 5	
C14	Can the laboratory differentiate MTB from other mycobacteria? *Please circle the number of the best response.*		YES NO	1 2	
C15	Is mycobacterial sensitivity testing available? *Please circle the number of the best response.*		Yes, all cultures Only if requested or after treatment failure or suspected relapse Not available	1 2 3 4	
C16	Is sensitivity testing available for 2nd line TB drugs? *Please circle the number of the best response.*		YES NO	1 2	

TO DIAGNOSE TB IN CHILDREN DO YOU ALSO USE...? *(circle answers in columns below)*

		Available	Where	Accessibility	
C16	**Gastric washing**	Yes No Not applicable	On site Off site Varies from facility to facility Not applicable	Without restrictions if indicated Only if the patient can afford it Not applicable	
C17	**Induced sputum**	Yes No Not applicable	On site Off site Varies from facility to facility Not applicable	Without restrictions if indicated Only if the patient can afford it Not applicable	
C18	**Naso-pharyngeal aspirate**	Yes No Not applicable	On site Off site Varies from facility to facility Not applicable	Without restrictions if indicated Only if the patient can afford it Not applicable	

FOR MANAGEMENT OF ACTIVE TUBERCULOSIS ...

	Please circle the number of the best responses for ADULTS and for CHILDREN	FOR ADULTS		FOR CHILDREN		
C19	Is a tuberculin skin test (TST) result available for...? *Please circle the number of the best response.*	For all TB patients Only for AFB smear negative Other (specify)_____ Not available at this site	1 2 3 4	For all TB patients Only for AFB smear negative Other (specify)_____ Not available at this site	1 2 3 4	

	Please circle the number of the best responses for ADULTS and for CHILDREN	FOR ADULTS		FOR CHILDREN		
C20	What guidelines do you predominantly use to manage TB patients? *Please circle the number(s) of the best responses.*	WHO National Local Other (specify)_____ None	1 2 3 4 5	WHO National Local Other (specify)_____ None	1 2 3 4 5	
C21	What is your 1st line TB treatment for new patients in the INITIAL PHASE? *Please circle the number of the best response.*	Isoniazid (H) Rifampicin (R) Pyrazinamide (Z) Streptomycin (S) Ethambutol (E) Thioacetazone (T) Other (specify)_____	1 2 3 4 5 6 7	Isoniazid (H) Rifampicin (R) Pyrazinamide (Z) Streptomycin (S) Ethambutol (E) Thioacetazone (T) Other (specify)_____	1 2 3 4 5 6 7	
C22	What is your 1st line TB treatment for patients in the CONTINUATION PHASE? *Please circle the number of the best response.*	Isoniazid (H) Rifampicin (R) Pyrazinamide (Z) Streptomycin (S) Ethambutol (E) Thioacetazone (T) Other(specify)_____	1 2 3 4 5 6 7	Isoniazid (H) Rifampicin (R) Pyrazinamide (Z) Streptomycin (S) Ethambutol (E) Thioacetazone (T) Other(specify)_____	1 2 3 4 5 6 7	
C23	Are patients taking TB treatment routinely observed as per the DOTS approach? *Please circle the number of the best response.*	In the first 2 months During the entire period NO	1 2 3	In the first 2 months During the entire period NO	1 2 3	
C24	What is the initial ART regimen for on TB treatment?	For ADULTS _____ _____		FOR CHILDREN _____ _____		

CANCER SECTION:

D. CANCER. Please answer these cancer-related questions about HIV patients treated at this facility. "UNIT" refers to the cancer care location for persons with HIV.

No.	QUESTIONS AND INSTRUCTIONS	RESPONSES	SKIPS
	Questions D01—D10 are about case ascertainment of cancer cases, including sources of cancer data, their validity, and completeness.		
D01	How would you describe your unit? Circle the number(s) for the best response(s).	Individual medical clinic ☐ Group of medical clinics ☐ Center from a multi-site study ☐ Academic hospital ☐ Other hospital (local, non teaching, etc.) ☐ Other, Please describe: _____	

D02

Please indicate the type of patients seen in your unit by choosing the approximate percentage of all patients seen in your unit for each category listed below:

HIV patients	☐0%	☐ 1-25%	☐ 26-49%	☐ 50-75%	☐> 75%
Cancer patients	☐0%	☐ 1-25%	☐ 26-49%	☐ 50-75%	☐> 75%
Infectious Disease	☐0%	☐ 1-25%	☐ 26-49%	☐ 50-75%	☐> 75%
Surgical patients	☐0%	☐ 1-25%	☐ 26-49%	☐ 50-75%	☐> 75%
Other: _____	☐0%	☐ 1-25%	☐ 26-49%	☐ 50-75%	☐> 75%
Other: _____	☐0%	☐ 1-25%	☐ 26-49%	☐ 50-75%	☐> 75%
Other: _____	☐0%	☐ 1-25%	☐ 26-49%	☐ 50-75%	☐> 75%
Other: _____	☐0%	☐ 1-25%	☐ 26-49%	☐ 50-75%	☐> 75%
Other: _____	☐0%	☐ 1-25%	☐ 26-49%	☐ 50-75%	☐> 75%

D03	What is the earliest year your unit begin collecting cancer data? Specify year.	*Specify year below.* _____ Unknown	9
D04	What is the most recent year for which your unit collected cancer data? Specify year.	*Specify year below.* _____ Unknown	9

D05 A list of several common cancer types in HIV-patients is provided in the table below. Please estimate the % each cancer type is seen in your unit among all cancers diagnosed. Space is provided at the end of the table if needed for additional cancer types that are common to HIV-infected patients in your unit.

Estimate the percentage that each of the following cancer types is found among all people with cancer in your unit. If needed, list other cancer types commonly seen in your unit. (Select one answer that most applies for each type of cancer):					
Anal	☐ 0%	☐ 1-5%	☐ 6-20%	☐ 20-75%	☐ > 75%
Breast	☐ 0%	☐ 1-5%	☐ 6-20%	☐ 20-75%	☐ > 75%
Cervix	☐ 0%	☐ 1-5%	☐ 6-20%	☐ 20-75%	☐ > 75%
Colorectal	☐ 0%	☐ 1-5%	☐ 6-20%	☐ 20-75%	☐ > 75%
Head and Neck	☐ 0%	☐ 1-5%	☐ 6-20%	☐ 20-75%	☐ > 75%
Hodgkin's Disease	☐ 0%	☐ 1-5%	☐ 6-20%	☐ 20-75%	☐ > 75%
Non-Hodgkin's Lymphoma	☐ 0%	☐ 1-5%	☐ 6-20%	☐ 20-75%	☐ > 75%
Kaposi's Sarcoma	☐ 0%	☐ 1-5%	☐ 6-20%	☐ 20-75%	☐ > 75%
Leukemia (Bone Marrow)	☐ 0%	☐ 1-5%	☐ 6-20%	☐ 20-75%	☐ > 75%
Liver	☐ 0%	☐ 1-5%	☐ 6-20%	☐ 20-75%	☐ > 75%
Lung	☐ 0%	☐ 1-5%	☐ 6-20%	☐ 20-75%	☐ > 75%
Penis	☐ 0%	☐ 1-5%	☐ 6-20%	☐ 20-75%	☐ > 75%
Prostate	☐ 0%	☐ 1-5%	☐ 6-20%	☐ 20-75%	☐ > 75%
Stomach	☐ 0%	☐ 1-5%	☐ 6-20%	☐ 20-75%	☐ > 75%
Other:	☐ 0%	☐ 1-5%	☐ 6-20%	☐ 20-75%	☐ > 75%
Other: _____	☐ 0%	☐ 1-5%	☐ 6-20%	☐ 20-75%	☐ > 75%
Other:	☐ 0%	☐ 1-5%	☐ 6-20%	☐ 20-75%	☐ > 75%
Other:	☐ 0%	☐ 1-5%	☐ 6-20%	☐ 20-75%	☐ > 75%
Other: _____	☐ 0%	☐ 1-5%	☐ 6-20%	☐ 20-75%	☐ > 75%

D06 **Estimate the percentage (%) of the use of tissue sampling (biopsy or fine needle aspiration) in the diagnosis or staging of each of the following cancer types in your unit. If needed, list other cancer types commonly seen in your unit. Space is provided at the end of the table for a listing of additional cancer types that are common to HIV-infected patients in your unit.**

Estimate the percentage that each of the following cancer types is found among all people with cancer in your unit. If needed, list other cancer types commonly seen in your unit. (select one answer that most applies for each cancer type):					
Anal	☐ 0%	☐ 1-5%	☐ 6-20%	☐ 20-75%	☐ > 75%
Breast	☐ 0%	☐ 1-5%	☐ 6-20%	☐ 20-75%	☐ > 75%
Cervix	☐ 0%	☐ 1-5%	☐ 6-20%	☐ 20-75%	☐ > 75%
Colorectal	☐ 0%	☐ 1-5%	☐ 6-20%	☐ 20-75%	☐ > 75%
Head and Neck	☐ 0%	☐ 1-5%	☐ 6-20%	☐ 20-75%	☐ > 75%
Hodgkin's Disease	☐ 0%	☐ 1-5%	☐ 6-20%	☐ 20-75%	☐ > 75%
Non-Hodgkin's Lymphoma	☐ 0%	☐ 1-5%	☐ 6-20%	☐ 20-75%	☐ > 75%
Kaposi's Sarcoma	☐ 0%	☐ 1-5%	☐ 6-20%	☐ 20-75%	☐ > 75%
Leukemia (Bone Marrow)	☐ 0%	☐ 1-5%	☐ 6-20%	☐ 20-75%	☐ > 75%
Liver	☐ 0%	☐ 1-5%	☐ 6-20%	☐ 20-75%	☐ > 75%
Lung	☐ 0%	☐ 1-5%	☐ 6-20%	☐ 20-75%	☐ > 75%
Penis	☐ 0%	☐ 1-5%	☐ 6-20%	☐ 20-75%	☐ > 75%
Prostate	☐ 0%	☐ 1-5%	☐ 6-20%	☐ 20-75%	☐ > 75%
Stomach	☐ 0%	☐ 1-5%	☐ 6-20%	☐ 20-75%	☐ > 75%
Other:	☐ 0%	☐ 1-5%	☐ 6-20%	☐ 20-75%	☐ > 75%
Other:	☐ 0%	☐ 1-5%	☐ 6-20%	☐ 20-75%	☐ > 75%
Other:	☐ 0%	☐ 1-5%	☐ 6-20%	☐ 20-75%	☐ > 75%
Other:	☐ 0%	☐ 1-5%	☐ 6-20%	☐ 20-75%	☐ > 75%
Other:	☐ 0%	☐ 1-5%	☐ 6-20%	☐ 20-75%	☐ > 75%

D07

Estimate the percentage of the use of radiograph (X-ray) in the diagnosis or staging of each of the following cancer types in your unit. If needed, list other cancer types commonly seen in your unit. (Select one answer that most applies for each cancer type):					
Breast	☐ Never	☐ Rarely (0-25%)	☐ Sometimes (25-75%)	☐ Often (>75-99%)	☐ Always
Colorectal	☐ Never	☐ Rarely (0-25%)	☐ Sometimes (25-75%)	☐ Often (>75-99%)	☐ Always
Head and Neck	☐ Never	☐ Rarely (0-25%)	☐ Sometimes (25-75%)	☐ Often (>75-99%)	☐ Always
Hodgkin's Disease	☐ Never	☐ Rarely (0-25%)	☐ Sometimes (25-75%)	☐ Often (>75-99%)	☐ Always
Non-Hodgkin's Lymphoma	☐ Never	☐ Rarely (0-25%)	☐ Sometimes (25-75%)	☐ Often (>75-99%)	☐ Always
Liver	☐ Never	☐ Rarely (0-25%)	☐ Sometimes (25-75%)	☐ Often (>75-99%)	☐ Always
Lung	☐ Never	☐ Rarely (0-25%)	☐ Sometimes (25-75%)	☐ Often (>75-99%)	☐ Always
Stomach	☐ Never	☐ Rarely (0-25%)	☐ Sometimes (25-75%)	☐ Often (>75-99%)	☐ Always
Other: _____	☐ Never	☐ Rarely (0-25%)	☐ Sometimes (25-75%)	☐ Often (>75-99%)	☐ Always
Other: _____	☐ Never	☐ Rarely (0-25%)	☐ Sometimes (25-75%)	☐ Often (>75-99%)	☐ Always
Other: _____	☐ Never	☐ Rarely (0-25%)	☐ Sometimes (25-75%)	☐ Often (>75-99%)	☐ Always
Other: _____	☐ Never	☐ Rarely (0-25%)	☐ Sometimes (25-75%)	☐ Often (>75-99%)	☐ Always
Other: _____	☐ Never	☐ Rarely (0-25%)	☐ Sometimes (25-75%)	☐ Often (>75-99%)	☐ Always

D08

Estimate the percentage of the use of radiograph (ultrasound or computerized tomography) in the diagnosis or staging of each of the following cancer types in your unit. If needed, list other cancer types commonly seen in your unit. (Select one answer that most applies for each cancer type):					
Breast	☐Never	☐Rarely (0-25%)	☐Sometimes (25-75%)	☐Often (>75-99%)	☐Always
Cervix	☐Never	☐Rarely (0-25%)	☐Sometimes (25-75%)	☐Often (> 75-99%)	☐Always
Colorectal	☐Never	☐Rarely (0-25%)	☐Sometimes (25-75%)	☐Often (> 75-99%)	☐Always
Head and Neck	☐Never	☐Rarely (0-25%)	☐Sometimes (25-75%)	☐Often (> 75-99%)	☐Always
Hodgkin's Disease	☐Never	☐Rarely (0-25%)	☐Sometimes (25-75%)	☐Often (> 75-99%)	☐Always
Non-Hodgkin's Lymphoma	☐Never	☐Rarely (0-25%)	☐Sometimes (25-75%)	☐Often (> 75-99%)	☐Always
Liver	☐Never	☐Rarely (0-25%)	☐Sometimes (25-75%)	☐Often (> 75-99%)	☐Always
Lung	☐Never	☐Rarely (0-25%)	☐Sometimes (25-75%)	☐Often (> 75-99%)	☐Always
Prostate	☐Never	☐Rarely (0-25%)	☐Sometimes (25-75%)	☐Often (> 75-99%)	☐Always
Stomach	☐Never	☐Rarely (0-25%)	☐Sometimes (25-75%)	☐Often (> 75-99%)	☐Always
Other:	☐Never	☐Rarely (0-25%)	☐Sometimes (25-75%)	☐Often (> 75-99%)	☐Always
Other:	☐Never	☐Rarely (0-25%)	☐Sometimes (25-75%)	☐Often (> 75-99%)	☐Always
Other:	☐Never	☐Rarely (0-25%)	☐Sometimes (25-75%)	☐Often (> 75-99%)	☐Always
Other:	☐Never	☐Rarely (0-25%)	☐Sometimes (25-75%)	☐Often (> 75-99%)	☐Always
Other:	☐Never	☐Rarely (0-25%)	☐Sometimes (25-75%)	☐Often (> 75-99%)	☐Always

D09

Estimate the percentage of the use of endoscopic procedures (e.g., upper aerodigestive endoscopy, colonoscopy, cystoscopy, bronchoscopy) in the diagnosis or staging of each of the following cancer types in your unit. If needed, list other cancer types commonly seen in your unit. (Select one answer that most applies for each cancer type):					
Anal	☐Never	☐Rarely (0-25%)	☐Sometimes (25-75%)	☐Often (> 75-99%)	☐Always
Cervix	☐Never	☐Rarely (0-25%)	☐Sometimes (25-75%)	☐Often (> 75-99%)	☐Always
Colorectal	☐Never	☐Rarely (0-25%)	☐Sometimes (25-75%)	☐Often (> 75-99%)	☐Always
Head and Neck	☐Never	☐Rarely (0-25%)	☐Sometimes (25-75%)	☐Often (> 75-99%)	☐Always
Lung	☐Never	☐Rarely (0-25%)	☐Sometimes (25-75%)	☐Often (> 75-99%)	☐Always
Stomach	☐Never	☐Rarely (0-25%)	☐Sometimes (25-75%)	☐Often (> 75-99%)	☐Always
Other:	☐Never	☐Rarely (0-25%)	☐Sometimes (25-75%)	☐Often (> 75-99%)	☐Always
Other:	☐Never	☐Rarely (0-25%)	☐Sometimes (25-75%)	☐Often (> 75-99%)	☐Always
Other:	☐Never	☐Rarely (0-25%)	☐Sometimes (25-75%)	☐Often (> 75-99%)	☐Always
Other:	☐Never	☐Rarely (0-25%)	☐Sometimes (25-75%)	☐Often (> 75-99%)	☐Always
Other:	☐Never	☐Rarely (0-25%)	☐Sometimes (25-75%)	☐Often (> 75-99%)	☐Always

D10

Please estimate the percentage of patients in your unit for whom you collect the following information (0- 100%) and in which form is this information stored (check all that apply):		
Information on:	**% of patients in your unit for whom you collect this information (0- 100%)**	**In which form is this information stored (check all that apply):**
Cancer diagnoses (as Yes/No)		☐ Paper medical chart kept by patient ☐ Paper medical chart kept by unit ☐ Electronic data
Specific cancer types		☐ Paper medical chart kept by patient ☐ Paper medical chart kept by unit ☐ Electronic data
Histopathology		☐ Paper medical chart kept by patient ☐ Paper medical chart kept by unit ☐ Electronic data
Radiologic information		☐ Paper medical chart kept by patient ☐ Paper medical chart kept by unit ☐ Electronic data
Computerized tomography		☐ Paper medical chart kept by patient ☐ Paper medical chart kept by unit ☐ Electronic data
Endoscopic information		☐ Paper medical chart kept by patient ☐ Paper medical chart kept by unit ☐ Electronic data

Questions D11- D13 are about common risk factors for cancer, including behaviors such as smoking, alcohol use, sexual behavior and co-infections.

D11 Please check the boxes in the table below for risk factors which may be collected within your unit.

Behavior/Other risk factors	Do you collect any information for this behavior?	If yes,do you normally ask about the frequency and/or quantity?
Cigarette smoking	☐ Yes; ☐ No	☐ Yes; ☐ No
Pipe smoking	☐ Yes; ☐ No	☐ Yes; ☐ No
Tobacco chewing	☐ Yes; ☐ No	☐ Yes; ☐ No
Wood burning stove	☐ Yes; ☐ No	☐ Yes; ☐ No
Alcohol consumption	☐ Yes; ☐ No	☐ Yes; ☐ No
Lifetime or recent # of sex partners	☐ Yes; ☐ No	☐ Yes; ☐ No
Same sex or opposite sex partner preference	☐ Yes; ☐ No	
Snuff	☐ Yes; ☐ No	☐ Yes; ☐ No
Illicit/illegal injection drug use	☐ Yes; ☐ No	☐ Yes; ☐ No
Marijuana/cannabis	☐ Yes; ☐ No	☐ Yes; ☐ No
Illicit/illegal non-injection drug use	☐ Yes; ☐ No	☐ Yes; ☐ No
Family history of cancer	☐ Yes; ☐ No	

D12 **Please check the boxes in the table below for co-infections/laboratory measures which may be collected within your unit.**

Co-infection or laboratory measure	Do you collect any information for this co-infection or laboratory measure?	If yes, what is the method of diagnoses (select all that apply):
KSHV	☐ Yes; ☐ No	☐ Serology ☐ PCR
Hepatitis B	☐ Yes; ☐ No	☐ Serology ☐ PCR
Hepatitis C	☐ Yes; ☐ No	☐ Serology ☐ PCR
Epstein-Bar virus	☐ Yes; ☐ No	☐ Serology ☐ PCR
HPV	☐ Yes; ☐ No	☐ Serology ☐ PCR
HTLV-1	☐ Yes; ☐ No	☐ Serology ☐ PCR
H. pylori	☐ Yes; ☐ No	☐ Serology ☐ PCR
Malaria	☐ Yes; ☐ No	☐ Serology ☐ PCR
TB	☐ Yes; ☐ No	

D13

Please estimate the percentage of patients in your unit for whom you collect the following information (0- 100%) and in which form is this information stored (check all that apply):		
Information on:	% of patients in your unit for whom you collect this information (0- 100%)	In which form is this information stored (check all that apply):
Behavior/Other risk factors		☐ Paper medical chart kept by patient ☐ Paper medical chart kept by unit ☐ Electronic data
Co-infections		☐ Paper medical chart kept by patient ☐ Paper medical chart kept by unit ☐ Electronic data
Laboratory measures		☐ Paper medical chart kept by patient ☐ Paper medical chart kept by unit ☐ Electronic data

	Is this diagnostic method used for cancer screening in your unit?	If diagnostic method is available, indicate the main reason someone may not use this method. *Please check the box beside all that apply.*	
D14	**Mammograms** ☐ Method not available ☐ Available, used for diagnosis only ☐ Available, used for diagnosis and screening	☐ High cost to the patient ☐ Logistics (e.g. patient lives far away from closest facility.) ☐ High waiting time to receive test ☐ Other_____ ☐ Don't Know ☐ NA	
D15	**Prostate-specific antigen** ☐ Method not available ☐ Available, used for diagnosis only ☐ Available, used for diagnosis and screening	☐ High cost to the patient ☐ Logistics (e.g. patient lives far away from closest facility.) ☐ High waiting time to receive test ☐ Other_____ ☐ Don't Know ☐ NA	

	Is this diagnostic method used for cancer screening in your unit?	If diagnostic method is available, indicate the main reason someone may not use this method. *Please check the box beside all that apply.*	
D16	**Cervical Pap smear** ☐ Method not available ☐ Available, used for diagnosis only ☐ Available, used for diagnosis and screening	☐ High cost to the patient ☐ Logistics (e.g. patient lives far away from closest facility.) ☐ High waiting time to receive test ☐ Other_____ ☐ Don't Know ☐ NA	
D17	**Gynecologic exam (visual inspection only with ascetic acid)** ☐ Method not available ☐ Available, used for diagnosis only ☐ Available, used for diagnosis and screening	☐ High cost to the patient ☐ Logistics (e.g. patient lives far away from closest facility.) ☐ High waiting time to receive test ☐ Other_____ ☐ Don't Know ☐ NA	
D18	**Anal Pap smear** ☐ Method not available ☐ Available, used for diagnosis only ☐ Available, used for diagnosis and screening	☐ High cost to the patient ☐ Logistics (e.g. patient lives far away from closest facility.) ☐ High waiting time to receive test ☐ Other_____ ☐ Don't Know ☐ NA	
D19	**Ultra sound** ☐ Method not available ☐ Available, used for diagnosis only ☐ Available, used for diagnosis and screening	☐ High cost to the patient ☐ Logistics (e.g. patient lives far away from closest facility.) ☐ High waiting time to receive test ☐ Other_____ ☐ Don't Know ☐ NA	
D20	**Occult blood in stool** ☐ Method not available ☐ Available, used for diagnosis only ☐ Available, used for diagnosis and screening	☐ High cost to the patient ☐ Logistics (e.g. patient lives far away from closest facility.) ☐ High waiting time to receive test ☐ Other_____ ☐ Don't Know ☐ NA	
D21	**Colonoscopy** ☐ Method not available ☐ Available, used for diagnosis only ☐ Available, used for diagnosis and screening	☐ High cost to the patient ☐ Logistics (e.g. patient lives far away from closest facility.) ☐ High waiting time to receive test ☐ Other_____ ☐ Don't Know ☐ NA	

D22	**Chest x-ray** ☐ Method not available ☐ Available, used for diagnosis only ☐ Available, used for diagnosis and screening	☐ High cost to the patient ☐ Logistics (e.g. patient lives far away from closest facility.) ☐ High waiting time to receive test ☐ Other_____ ☐ Don't Know ☐ NA	
D23	**Alpha-fetoprotein blood test** ☐ Method not available ☐ Available, used for diagnosis only ☐ Available, used for diagnosis and screening	High cost to the patient ☐ Logistics (e.g. patient lives far away from closest facility.) ☐ High waiting time to receive test ☐ Other_____ ☐ Don't Know ☐ NA	
D24	Are data regarding these diagnostic methods available for your unit? *Please circle the number of the best response.*	☐Yes ☐ No	

	Questions D25-D41 refer to available data on cancer treatments and outcomes among your cohort members. *Please check the box next to the best response.*		
D25	Are data regarding chemotherapy available for your unit?	☐Yes ☐ No	
D26	Are data regarding radiotherapy available for your unit?	☐Yes ☐ No	
D27	Are data regarding surgery available for your unit?	☐Yes ☐ No	
D28	Are data regarding comfort care (e.g., antiemetic or other supportive therapy) available for your unit?	☐Yes ☐ No	
D29	Are data regarding palliative care (e.g., analgesic therapy and other treatment modalities when cure can no longer be attempted) available for your unit?	☐Yes ☐ No	
D30	Are data regarding hormonal therapy available for treatment of prostate and breast cancer available for your unit?	☐Yes ☐ No	
	Please rate how strongly you agree or disagree with following statements:		
D31	Estimate the percentage of the use of chemotherapy for cancer patients that need it.	☐ Never ☐ Rarely (0<25%) ☐ Sometimes (25%<75%) ☐ Often (75% > but not always) ☐ Always (100%)	

D32	Please select the main reason someone with cancer may not receive chemotherapy if they need it.	☐ High cost to the patient ☐ Logistics (e.g. patient lives far away from closest facility.) ☐ High waiting time to receive test ☐ Other_____ ☐ Don't Know	
D33	Estimate the percentage of the use of radiotherapy for cancer patients that need it.	☐ Never ☐ Rarely (0<25%) ☐ Sometimes (25%<75%) ☐ Often (75% > but not always) ☐ Always (100%)	
D34	Please select the main reason someone with cancer may not receive radiotherapy if they need it.	☐ High cost to the patient ☐ Logistics (e.g. patient lives far away from closest facility.) ☐ High waiting time to receive test ☐ Other_____ ☐ Don't Know	
D35	Estimate the percentage of the use of surgery for cancer patients that need it.	☐ Never ☐ Rarely (0<25%) ☐ Sometimes (25%<75%) ☐ Often (75% > but not always) ☐ Always (100%)	
D36	Please select the main reason someone with cancer may not receive surgery if they need it.	☐ High cost to the patient ☐ Logistics (e.g. patient lives far away from closest facility.) ☐ High waiting time to receive test ☐ Other_____ ☐ Don't Know	
D37	Estimate the percentage of the use of palliative care for cancer patients that need it.	☐ Never ☐ Rarely (0<25%) ☐ Sometimes (25%<75%) ☐ Often (75% > but not always) ☐ Always (100%)	
D38	Please select the main reason someone with cancer may not receive palliative care if they need it.	☐ High cost to the patient ☐ Logistics (e.g. patient lives far away from closest facility.) ☐ High waiting time to receive test ☐ Other_____ ☐ Don't Know	
D39	Estimate the percentage of the use of hormonal therapy for all prostate and breast cancer patients that need it.	☐ Never ☐ Rarely (0<25%) ☐ Sometimes (25%<75%) ☐ Often (75% > but not always) ☐ Always (100%)	
D40	Please select the main reason someone with prostate or breast cancer may not receive hormal therapy if they need it.	☐ High cost to the patient ☐ Logistics (e.g. patient lives far away from closest facility.) ☐ High waiting time to receive test ☐ Other_____ ☐ Don't Know	

D41

Please estimate the percentage of patients in your unit for whom you collect the following information (0-100%) and in which form is this information stored (check all that apply):		
Information on:	**% of patients in your unit for whom you collect this information (0- 100%)**	**In which form is this information stored (check all that apply):**
Surgery		☐ Paper medical chart kept by patient ☐ Paper medical chart kept by unit ☐ Electronic data
Chemotherapy		☐ Paper medical chart kept by patient ☐ Paper medical chart kept by unit ☐ Electronic data
Radiotherapy		☐ Paper medical chart kept by patient ☐ Paper medical chart kept by unit ☐ Electronic data
Hormonal therapy		☐ Paper medical chart kept by patient ☐ Paper medical chart kept by unit ☐ Electronic data
Comfort care		☐ Paper medical chart kept by patient ☐ Paper medical chart kept by unit ☐ Electronic data
Palliative care		☐ Paper medical chart kept by patient ☐ Paper medical chart kept by unit ☐ Electronic data

	Questions D42-D44 relate to the collection of mortality data on cancer patients in your facility		
D42	Are data available for date of death for cancer patients in your unit?	*Please check the box next to the best response.* ☐ Yes ☐ No	
D43	Are data available for cause of death for cancer patients in your unit?	*Please check the box next to the best response.* ☐ Yes ☐ No	
D44	Please indicate sources of mortality data from the following list (circle the number(s) for all that apply):	☐ Medical records ☐ Administrative databases ☐ Death certificates ☐ National mortality databases ☐ Other. Please describe: _____	

IeDEA Pediatric Site Assessment Survey

Version: November 25, 2008

A. Contact information	
Name of Clinic	Other contact: (email/phone)
Name of Primary Contact Pediatrician	Database manager
Address	Email
Telephone	Name of person completing questionnaire
Fax	Date questionnaire completed

B. About the Clinic *Please check the box of the best response(s) or complete blanks where provided..*		
B01	Type of facility: ☐ Public (government) ☐ Private not for profit (NGO) ☐ Private, for profit ☐ Academic ☐ Other:	
B02	What best describes your site: ☐ HIV outpatient clinic in a hospital ☐ Free-standing HIV clinic ☐ Family practice clinic ☐ PMTCT clinic ☐ Tuberculosis clinic ☐ Antiretroviral-specific clinic ☐ Research site ☐ Other:	
B03	B03. Location: ☐ urban ☐ rural ☐ in-between	
B04	B04. What is the availability of Internet and e-mail at the facility? ☐ On-site and within care & treatment facility ☐ On-site but outside care & treatment facility ☐ Off-site but within 5 km of site ☐ No access on-site or within 5 km ☐ Other:	
B05	5. Does site maintain electronic medical records and database? ☐ Yes with electronic medical records and on-site electronic database ☐ Yes with paper medical records and on-site electronic database ☐ No paper medical records transferred to off-site central database ☐ No ☐ Other:	
B06	6. What patients are seen in this clinic? ☐ children only ☐ adults and children in separate clinics ☐ adults and children in combined family clinics	

B. About the Clinic *Please check the box of the best response(s) or complete blanks where provided..*

B07	What is the upper age limit of children attending the children's clinic (after which they attend an adult clinic)? _____ years old	
B08	How many half-day clinic sessions for HIV-exposed and –infected children are there per week?_____ days	
B09	a. Does your facility serve: ☐ HIV-exposed & -infected children ☐ HIV-infected children only ☐ HIV-infected adults & children ☐ other, specify: b. Does your facility serve pregnant HIV-infected women? ☐ yes ☐ no	

B10. Do patients need to pay for costs of following care & services? (check all that apply)

a. Screening consult:	☐ No (free)	☐ Yes – full pay	☐ Yes – partial pay	☐ not available
b. Laboratory tests:	☐ No (free)	☐ Yes – full pay	☐ Yes – partial pay	☐ not available
c. Diagnostic exams:	☐ No (free)	☐ Yes – full pay	☐ Yes – partial pay	☐ not available
d. 1st-line ART:	☐ No (free)	☐ Yes – full pay	☐ Yes – partial pay	☐ not available
e. 2nd-line ART:	☐ No (free)	☐ Yes – full pay	☐ Yes – partial pay	☐ not available
f. OI prophylaxis/treatment	☐ No (free)	☐ Yes – full pay	☐ Yes – partial pay	☐ not available
g. Routine follow-up consult	☐ No (free)	☐ Yes – full pay	☐ Yes – partial pay	☐ not available
h. Additional consults	☐ No (free)	☐ Yes – full pay	☐ Yes – partial pay	☐ not available
i. Travel to clinic	☐ No (free)	☐ Yes – full pay	☐ Yes – partial pay	☐ not available

B11	Source(s) of funding for services and care *(check all that apply)*: ☐ government ☐ patient fees ☐ Global Fund ☐ PEPFAR ☐ MSF ☐ research (NIH, ANRS, industry, etc.) ☐ other, specify:	
B12	Is each patient assigned a unique identifier? ☐ yes ☐ no	
B13	Is it possible to link child's records with mother's records? ☐ yes ☐ no	
B14	When did clinic start seeing HIV-exposed/-infected children? _____(YEAR)	
B15	When did clinic start providing ART to children? _____(YEAR)	
B16	Over the previous 6 months what was the average number of HIV-exposed and –infected children attending each half-day clinic session? _____	
B17	Over the previous 6 months, what was the average number of children initiating ART each month? _____	
B18	Which of the following services are available for children? (check all that apply) ☐ HIV diagnosis ☐ Growth monitoring ☐ Immunization ☐ IMCI (Integrated Management of Childhood Illnesses) ☐ Cotrimoxazole for HIV-exposed infants ☐ None of the above	
B19	What nutritional support us available for children?	

	☐ Nutritional counseling ☐ Food for malnourished children ☐ Micronutrients/vitamin supplementation ☐ None of above	
B20	Do you provide the following nutritional supplementation for children? *Multivitamin* ☐ All infants of HIV+ mothers ☐ Only HIV-infected infants ☐ Only HIV-infected infants not ART ☐ specific clinical indications only *Vitamin A* ☐ All infants of HIV+ mothers ☐ Only HIV-infected infants ☐ Only HIV-infected infants not ART ☐ specific clinical indications only *Zinc* ☐ All infants of HIV+ mothers ☐ Only HIV-infected infants ☐ Only HIV-infected infants not ART ☐ specific clinical indications only Other (specify): _____	
B21	What psychosocial support is available for children? (check all that apply) ☐ General individual counseling ☐ Support groups for children ☐ Disclosure counseling for caretakers ☐ Disclosure counseling for children ☐ Other: _____ ☐ None	
B22	Total number of full time equivalents (FTEs) to care for children at your site: *Write number of hours for each below.* Pediatricians: _____ Medical doctors (non-pediatricians): _____ Nurses doing clinical work: _____ Counselors/social workers: _____ Pharmacists: _____ Pharmacy assistants: _____ Administrative staff: _____ Outreach workers: _____ Data capturers: _____	
C. Prevention of Mother-to-Child Transmission (PMTCT) Check the box of the correct response(s).		
C01	Do you routinely record history of PMTCT in children's records? ☐ Yes, when history is available ☐ No, but information is available ☐ No, information is not available	
C02	Do you provide perinatal services at your clinic? ☐ yes ☐ no (if no, skip to section IV)	

C. Prevention of Mother-to-Child Transmission (PMTCT) Check the box of the correct response(s).		
C03	What maternity services are available at your clinic (regardless of who pays)? ☐ HIV testing ☐ CD4+ count ☐ ART for treatment ☐ ART for PMTCT ☐ Pre-natal care ☐ Delivery ☐ Post-natal care ☐ None	
C04	Do pregnant women diagnosed with HIV in antenatal clinic get CD4 count to assess need for ART? ☐ Yes ☐ No	
C05	If eligible for ART treatment, do pregnant women: ☐ Receive ART at your clinic? ☐ Get referred to another ART clinic?	
C06	If available, what ART regimen(s) for PMTCT are used? (check all that apply) ☐ single-dose nevirapine (sdNVP) ☐ short-course AZT + sdNVP ☐ short-course AZT + sdNVP with AZT/3TC 7-day tail ☐ HAART (only for women who need treatment) ☐ HAART (for all women) ☐ Other:	
C07	What infant follow-up care is available after PMTCT at your clinic? ☐ Post-natal ARVs ☐ Infant formula ☐ Early infant diagnostic testing, i.e., by 8 weeks of age ☐ Cotrimoxazole until infection status confirmed or 12 months of age ☐ Other:	
C08	What infant feeding approach is most commonly recommended at your clinic? ☐ Exclusive breastfeeding until 4-6 months of age, then weaning and complementary foods ☐ Exclusive breastfeeding until 4-6 months of age, then continued breastfeeding with complementary foods ☐ Exclusive formula feeding ☐ Other:	
D. HIV & OI Diagnoses & Services		
D01	How do you routinely diagnose HIV infection in HIV-exposed children **less than 6 months** of age? ☐ Clinical criteria/IMCI algorithm ☐ HIV RNA assay ☐ HIV DNA PCR ☐ HIV P24 antigen assay ☐ Combination of above, specify: _____ ☐ Other:	

D. HIV & OI Diagnoses & Services		
D02	How do you routinely diagnose HIV infection in HIV-exposed children **6-12 months** of age? ☐ Clinical criteria/IMCI algorithm ☐ HIV RNA assay ☐ HIV DNA PCR ☐ HIV P24 antigen assay ☐ Combination of above, specify: _____ ☐ Other: _____	
D03	How do you routinely diagnose HIV infection in HIV-exposed children **12-18 months** of age? ☐ Clinical criteria/IMCI algorithm ☐ HIV RNA assay ☐ HIV DNA PCR ☐ HIV P24 antigen assay ☐ Combination of above, specify: _____ ☐ Other: _____	
D04	How do you routinely diagnose HIV infection in HIV-exposed children 18 months of age or older? ☐ Clinical criteria/IMCI algorithm ☐ 1 rapid test ☐ 2 rapid tests ☐ 1 ELISA ☐ 2 ELISA ☐ Western Blot ☐ Combination of above, specify: _____ ☐ Other: _____	
D05	What TB services are available for children? ☐ PPD testing ☐ Chest x-ray ☐ Diagnosis by AFB smear ☐ Diagnosis by AFB culture ☐ Drug susceptibility testing ☐ Primary prophylaxis ☐ Secondary prophylaxis ☐ Treatment ☐ DOT (directly-observed therapy) program ☐ Other: _____ ☐ None of above	
D06	What facilities do you have to obtain sputum from children with suspected TB? Gastric washing ☐ on site ☐ on referral ☐ not available Induced sputum ☐ on site ☐ on referral ☐ not available Spontaneous sputum ☐ on site ☐ on referral ☐ not available	
D07	In HIV-exposed/-infected children over 12 months of age with no history of *Pneumocystis jiroveci* pneumonia (PCP), when do you stop primary prophylaxis with cotrimoxazole? ☐ After 6 months of treatment and CD4 above 15% ☐ After 6-12 months of treatment and CD4 above 15% ☐ After 12 months of treatment and CD4 above 15% ☐ On case-by-case basis without standard protocol ☐ Do not stop PCP prophylaxis ☐ Other:	

	_____	
D08	How do you diagnose malaria? ☐ Do not diagnose ☐ Smear ☐ Clinical judgment only ☐ Rapid test	
E. Laboratory facilities		
E01	Availability and turn-around time of laboratory tests *TEST* *AVAILABILITY* *TURN-AROUND* a. HIV RNA PCR: ☐ on site ☐ off site ☐ unavailable _____ days b. HIV DNA PCR: ☐ on site ☐ off site ☐ unavailable _____ days c. CD4 count: ☐ on site ☐ off site ☐ unavailable _____ days d. Hemoglobin: ☐ on site ☐ off site ☐ unavailable _____ days e. Total lymphs: ☐ on site ☐ off site ☐ unavailable _____ days f. ALT/AST: ☐ on site ☐ off site ☐ unavailable _____ days g. Cholesterol: ☐ on site ☐ off site ☐ unavailable _____ days h. Creatinine: ☐ on site ☐ off site ☐ unavailable _____ days	
E02	Which CD4 assay(s) is available? (check all that apply) ☐ Flow cytometry ☐ Facscan ☐ FACSCalibur ☐ Truecount ☐ PLG ☐ Calculation based on WBC and/or TLC ☐ Other: _____ ☐ None	
E03	41. Which HIV viral load assay(s) is available? (check all that apply) ☐ bDNA ☐ Roche Amplicor ☐ Nucleisens Biomerieux (ex-Nasba) ☐ Other: _____ ☐ None	
E04	If available, what is the lower limit of detection of HIV RNA assay routinely used at your site (check only one) ☐ <500 copies/ml ☐ <400 copies/ml ☐ <50 copies/ml ☐ <20 copies/ml ☐ <10 copies/ml ☐ Other ☐ Don't know	
E05	At your site, when are the following parameters monitored in children? a. CD4 count: ☐ Baseline ☐ Regular intervals: (_____months) ☐ not done b. Viral load: ☐ Baseline ☐ Regular intervals: (_____months) ☐ not done c. Weight: ☐ Baseline ☐ Regular intervals: (_____months) ☐ not done d. Height: ☐ Baseline ☐ Regular intervals: (_____months) ☐ not done e. Hemoglobin: ☐ Baseline ☐ Regular intervals: (_____months) ☐ not done f. Lymphocyte: ☐ Baseline ☐ Regular intervals: (_____months) ☐ not done g. ALT/AST: ☐ Baseline ☐ Regular intervals: (_____months) ☐ not done h. Creatinine: ☐ Baseline ☐ Regular intervals: (_____months) ☐ not done I. Cholesterol: ☐ Baseline ☐ Regular intervals: (_____months) ☐ not done	
F. About the HIV and antiretroviral therapy (ART) program		
F01	What are the 3 most common sources of referrals of pediatric patients to your facility? ☐ PMTCT program(s) ☐ Hospital in-patient ward(s) ☐ Out-patient clinic(s)	

	☐ Tuberculosis program/clinic(s) ☐ VCT program (e.g., as family or household member) ☐ Other: _____	
F02	Do you refer parents of HIV-infected children for HIV screening and/or treatment? ☐ Yes ☐ No	
F03	Do you refer siblings of HIV-infected children for HIV screening and/or treatment? ☐ Yes ☐ No	
F04	When do you evaluate stage of HIV infection for children: ☐ Baseline only ☐ At each follow-up visit ☐ At regular interval, specify: _____months ☐ Not done	
F05	Which staging system do you use for children? ☐ CDC ☐ WHO ☐ Both CDC and WHO ☐ Other: _____	
F06	How is dosing of drugs in children determined? (check all that apply) ☐ Weight (mg per kg) individual calculations ☐ Body surface area (mg per meter^2) individual calculations ☐ Use weight-band based dosing table ☐ Use age-band based dosing table ☐ Other:	
F07	What percentage of children regularly attending clinic need treatment but are not yet on it? _____%	
F08	Do you have a waiting list for initiating ART for children followed at your site? ☐ Yes ☐ No If yes, over the past 6 months what is the average waiting time for a child to initiate ART? ____days	
F09	Indications for initiating ART in children <u>What are indications for initiating ART for infected children ≤12 months?</u> ☐ All children get treated regardless of clinical or lab data ☐ Use CD4 & clinical criteria according to national/international guidelines ☐ Use clinical criteria alone ☐ Other: _____ <u>What are indications for initiating ART for infected children >12 months?</u> ☐ All children get treated regardless of clinical or lab data ☐ Use CD4 & clinical criteria according to national/international guidelines ☐ Use clinical criteria alone ☐ Other: _____	
F10	Do you offer adherence support such as treatment readiness or	

	counseling programs for children before starting ART? ☐ Yes ☐ No	
F11	How do you measure or assess adherence to treatment in children? ☐ 3-day recall ☐ Visual analog scale ☐ Pill count ☐ Viral load ☐ Other: _____ ☐ Do not routinely measure adherence	
F12	**Antiretroviral Treatments**	

ARV Name	How easy/difficult is it to access at your site?	Pediatric-specific formulation (e.g., liquid or pediatric-sized pill) available?	Generic available?
NRTIs			
Zidovudine (AZT)	☐ Easy ☐ Moderate ☐ Hard ☐ not available	☐ Yes ☐ No	☐ Yes ☐ No
Lamivudine (3TC)	☐ Easy ☐ Moderate ☐ Hard ☐ not available	☐ Yes ☐ No	☐ Yes ☐ No
Didanosine (ddI)	☐ Easy ☐ Moderate ☐ Hard ☐ not available	☐ Yes ☐ No	☐ Yes ☐ No
Stavudine (d4T)	☐ Easy ☐ Moderate ☐ Hard ☐ not available	☐ Yes ☐ No	☐ Yes ☐ No
Abacavir (ABC)	☐ Easy ☐ Moderate ☐ Hard ☐ not available	☐ Yes ☐ No	☐ Yes ☐ No
Tenofovir (TDF)	☐ Easy ☐ Moderate ☐ Hard ☐ not available	☐ Yes ☐ No	☐ Yes ☐ No
Emtricitibine (FTC)	☐ Easy ☐ Moderate ☐ Hard ☐ not available	☐ Yes ☐ No	☐ Yes ☐ No
NNRTIs			
Nevirapine (NVP)	☐ Easy ☐ Moderate ☐ Hard ☐ not available	☐ Yes ☐ No	☐ Yes ☐ No
Efavirenz (EFV)	☐ Easy ☐ Moderate ☐ Hard ☐ not available	☐ Yes ☐ No	☐ Yes ☐ No
PIs			
Lopinavir/ritonavir	☐ Easy ☐ Moderate ☐ Hard ☐ not available	☐ Yes ☐ No	☐ Yes ☐ No
Indinavir	☐ Easy ☐ Moderate ☐ Hard ☐ not available	☐ Yes ☐ No	☐ Yes ☐ No
Ritonavir	☐ Easy ☐ Moderate ☐ Hard ☐ not available	☐ Yes ☐ No	☐ Yes ☐ No
Saquinavir SGC	☐ Easy ☐ Moderate ☐ Hard ☐ not available	☐ Yes ☐ No	☐ Yes ☐ No
Saquinavir HGC	☐ Easy ☐ Moderate ☐ Hard ☐ not available	☐ Yes ☐ No	☐ Yes ☐ No
Nelfinavir	☐ Easy ☐ Moderate ☐ Hard ☐ not available	☐ Yes ☐ No	☐ Yes ☐ No
Atazanavir	☐ Easy ☐ Moderate ☐ Hard ☐ not available	☐ Yes ☐ No	☐ Yes ☐ No
Amprenavir	☐ Easy ☐ Moderate ☐ Hard ☐ not available	☐ Yes ☐ No	☐ Yes ☐ No
Fosamprenavir	☐ Easy ☐ Moderate ☐ Hard ☐ not available	☐ Yes ☐ No	☐ Yes ☐ No
Tipranavir	☐ Easy ☐ Moderate ☐ Hard ☐ not available	☐ Yes ☐ No	☐ Yes ☐ No
FDCs			
AZT/3TC	☐ Easy ☐ Moderate ☐ Hard ☐ not available	☐ Yes ☐ No	☐ Yes ☐ No
AZT/3TC/ABC	☐ Easy ☐ Moderate ☐ Hard ☐ not available	☐ Yes ☐ No	☐ Yes ☐ No
AZT/3TC/NVP	☐ Easy ☐ Moderate ☐ Hard ☐ not available	☐ Yes ☐ No	☐ Yes ☐ No
3TC/ABC	☐ Easy ☐ Moderate ☐ Hard ☐ not available	☐ Yes ☐ No	☐ Yes ☐ No
3TC/d4T/NVP	☐ Easy ☐ Moderate ☐ Hard ☐ not available	☐ Yes ☐ No	☐ Yes ☐ No
TDF/FTC	☐ Easy ☐ Moderate ☐ Hard ☐ not available	☐ Yes ☐ No	☐ Yes ☐ No
Others (not listed above - specify)			
	☐ Easy ☐ Moderate ☐ Hard ☐ not available	☐ Yes ☐ No	☐ Yes ☐ No
	☐ Easy ☐ Moderate ☐ Hard ☐ not available	☐ Yes ☐ No	☐ Yes ☐ No
	☐ Easy ☐ Moderate ☐ Hard ☐ not available	☐ Yes ☐ No	☐ Yes ☐ No
	☐ Easy ☐ Moderate ☐ Hard ☐ not available	☐ Yes ☐ No	☐ Yes ☐ No
	☐ Easy ☐ Moderate ☐ Hard ☐ not available	☐ Yes ☐ No	☐ Yes ☐ No

G.Patient Follow-up		
G01	In routine follow-up for a child, what is the frequency for seeing the following: Doctor ☐ every mo ☐ every 1-3 mos ☐ every 4-6 mos ☐ > every 6 mos ☐ never Nurse clinician Counselor/ ☐ every mo ☐ every 1-3 mos ☐ every 4-6 mos ☐ > every 6 mos ☐ never Social Work ☐ every mo ☐ every 1-3 mos ☐ every 4-6 mos ☐ > every 6 mos ☐ never Pharmacist ☐ every mo ☐ every 1-3 mos ☐ every 4-6 mos ☐ > every 6 mos ☐ never Pharmacy assistant ☐ every mo ☐ every 1-3 mos ☐ every 4-6 mos ☐ > every 6 mos ☐ never	
G02	What do you do if a child misses a visit? (check all that apply) ☐ Send a letter ☐ Telephone call ☐ Home visit by clinic staff ☐ Home visit by outreach workers (lay staff) ☐ Check hospital records ☐ Other: _____ ☐ Nothing	
G03	How do you define "lost to follow-up" in pediatric patients? ☐ Absence >3 months ☐ Absence >6 months ☐ Absence >12 months ☐ Depends upon whether the child is on or off cART. ☐ Other: _____	
G04	What, in your opinion, is the major cause of pediatric patients being lost to follow-up? ☐ Death ☐ Family lack of financial resources ☐ Lack of disclosure to family or neighbors ☐ Do not know ☐ Other, specify:	
G05	60. How do you ascertain deaths of children in your clinic? ☐ Family ☐ Word of mouth ☐ Physician report ☐ Data linkage with records at site ☐ Phone follow-up ☐ Home follow-up ☐ Not done ☐ Other: _____	

PEDIATRIC CANCER MODULE: The following questions try to ascertain how much cancer data recording occurs in the Pediatric setting.

Estimate the numbers of the following cancers presumptively or conclusively diagnosed among all pediatric HIV patients at your site within the previous five years. If a cancer type not included in the list, please specify type of cancer under "other" in the list below. (select one answer that most applies)

PC01	Burkitt 's Lymphoma	☐ 0	☐ 1-5	☐ 6-10	☐ >10	☐ Unknown
PC02	Retinoblastoma/Orbital Tumors	☐ 0	☐ 1-5	☐ 6-10	☐ >10	☐ Unknown
PC03	Kaposi's Sarcoma	☐ 0	☐ 1-5	☐ 6-10	☐ >10	☐ Unknown
PC04	Wilms Tumor	☐ 0	☐ 1-5	☐ 6-10	☐ >10	☐ Unknown
PC05	Non-Hodgkin's Lymphoma	☐ 0	☐ 1-5	☐ 6-10	☐ >10	☐ Unknown
PC06	Hodgkin's Disease	☐ 0	☐ 1-5	☐ 6-10	☐ >10	☐ Unknown
PC07	Leukemia	☐ 0	☐ 1-5	☐ 6-10	☐ >10	☐ Unknown
PC08	Neuroblastoma	☐ 0	☐ 1-5	☐ 6-10	☐ >10	☐ Unknown
PC09	Bone and Soft Tissue Sarcoma	☐ 0	☐ 1-5	☐ 6-10	☐ >10	☐ Unknown
PC10	Hepatic Tumor	☐ 0	☐ 1-5	☐ 6-10	☐ >10	☐ Unknown
PC11	HPV-Associated Cancer/Disease: Laryngeal Papillomatosis	☐ 0	☐ 1-5	☐ 6-10	☐ >10	☐ Unknown
PC12	HPV-Associated Cancer/Disease: Conjunctival carcinoma	☐ 0	☐ 1-5	☐ 6-10	☐ >10	☐ Unknown
PC13	HPV-Associated Cancer/Disease: Cervical Cancer	☐ 0	☐ 1-5	☐ 6-10	☐ >10	☐ Unknown
PC14	Other: _____	☐ 0	☐ 1-5	☐ 6-10	☐ >10	☐ Unknown
PC15	Other: _____	☐ 0	☐ 1-5	☐ 6-10	☐ >10	☐ Unknown
PC16	Other: _____	☐ 0	☐ 1-5	☐ 6-10	☐ >10	☐ Unknown

PC17	In what percentage of all of the diagnosed pediatric cancer cases noted above were the cancers treated with any available treatment modality (e.g., surgery, chemotherapy, radiation)?	☐<25%	☐25-49%	☐ 50-75%	☐>75-100%

If pediatric cancer treatment was available in the cases above, where did patients generally receive their cancer treatment? If cancer treatment was not available, skip to next question.						
PC18	Clinical site where HIV care is received	☐Never	☐Rarely (0-25%)	☐Sometimes (25-75%)	☐Often (> 75%-99%)	☐Always
PC19	Dedicated Cancer Center	☐Never	☐Rarely (0-25%)	☐Sometimes (25-75%)	☐Often (> 75%-99%)	☐Always
PC20	General Tertiary referral hospital	☐Never	☐Rarely (0-25%)	☐Sometimes (25-75%)	☐Often (> 75%-99%)	☐Always
PC21	Other location (specify)_____	☐Never	☐Rarely (0-25%)	☐Sometimes (25-75%)	☐Often (> 75%-99%)	☐Always
PC22	Other location (specify)_____	☐Never	☐Rarely (0-25%)	☐Sometimes (25-75%)	☐Often (> 75%-99%)	☐Always

Please estimate the frequency with which the following cancer treatment modalities were used for your pediatric HIV patients in the previous five years.						
PC23	Surgery alone	☐Never	☐Rarely (0-25%)	☐Sometimes (25-75%)	☐Often (> 75%-99%)	☐Always
PC24	Chemotherapy alone	☐Never	☐Rarely (0-25%)	☐Sometimes (25-75%)	☐Often (> 75%-99%)	☐Always
PC25	Radiation alone	☐Never	☐Rarely (0-25%)	☐Sometimes (25-75%)	☐Often (> 75%-99%)	☐Always
PC26	Surgery and Chemotherapy	☐Never	☐Rarely (0-25%)	☐Sometimes (25-75%)	☐Often (> 75%-99%)	☐Always
PC27	Surgery and Radiation	☐Never	☐Rarely (0-25%)	☐Sometimes (25-75%)	☐Often (> 75%-99%)	☐Always
PC28	Chemotherapy and Radiation	☐Never	☐Rarely (0-25%)	☐Sometimes (25-75%)	☐Often (> 75%-99%)	☐Always
PC29	Palliation (e.g., pain medication, nutritional supplementation)	☐Never	☐Rarely (0-25%)	☐Sometimes (25-75%)	☐Often (> 75%-99%)	☐Always
PC30	Other (specify) _____	☐Never	☐Rarely (0-25%)	☐Sometimes (25-75%)	☐Often (> 75%-99%)	☐Always

PC31	Other (specify) _____	☐Never	☐Rarely (0-25%)	☐Sometimes (25-75%)	☐Often (> 75%-99%)	☐Always

Which cancer treatment modalities are *currently* available to your pediatric HIV patients? (either at your site or a referral site) (Check all that apply)		
PC32	Surgery	☐
PC33	Chemotherapy	☐
PC34	Radiation	☐
PC35	Other (specify)_____	☐
PC36	None of the above	☐

PC37	If cancer-related diagnostic or treatment data are not available at your site, are the data available elsewhere (If yes, please specify).	☐Yes	If yes, specify: _____	☐ No

PC38	After their diagnosis, do patients with cancer continue to be followed up by your site for ongoing HIV care?	☐Yes	☐No

IeDEA East Africa Brief Follow-Up Questionnaire

This brief survey is a follow-up to the IeDEA site assessment tool. The aim of this survey is to gain a better understanding about:

1) **this facility's HIV-testing practices among asymptomatic individuals of unknown HIV-status, and**
2) **approaches to HIV care and treatment since it began providing HIV/AIDS care services.**

We plan to examine strategies aimed at earlier initiating of ART, and improving retention by encouraging disclosure, and social support. Specifically, we are focusing on the practice of active testing among asymptomatic sex partner(s), relatives and other household members of HIV/AIDS patients, and the implementation of the family-focused care model which centers on the health of the family not just the individual patient.

The survey is divided into three sections. Depending on the response, some questions may instruct you to skip to another question (see "SKIPS" column). You are encouraged to first read the entire document and then answer the questions. We greatly appreciate your participation.

Facility Name_____

Address: _____
Street

_____
City/District Region/State/Province

_____
Country

	Name/Email	Title/Position	No. of years working at this facility
Individual(s) Completing this Form	Name: Email:		
	Name: Email:		

Date this questionnaire was completed (DD/MM/YYYY): ☐☐/☐☐/☐☐☐☐

HIV/AIDS Care and Treatment Facility Questions

No.	Questions and Instructions	Responses	Skips
A01	When did this facility begin providing ART for adults?	*Please use the date format MM/YYYY* ☐☐/☐☐☐☐ **If the month is unknown please enter "99" for the month.**	
A02	When did this facility begin providing pre-ART HIV care to adults?	*Please use the date format MM/YYYY* ☐☐/☐☐☐☐ **If the month is unknown please enter "99" for the month.**	

Program Characteristics Part 1: The following questions pertain to the practice of active testing at this facility.

No.	Questions and Instructions	Responses		Skips
B01	**Active testing** is a programmatic activity where providers ask enrolled patients to bring in or refer their **asymptomatic**, undiagnosed relatives, sex partner(s), or other household members for HIV testing. **Where implemented, it forms part of a facility's protocol and it's a proactive effort by facility providers to reach out and test** specific, undiagnosed, **asymptomatic** HIV-infected individuals associated with enrolled patients. By providers we mean any member of the medical staff (e.g. doctors, nurses, counselors, pharmacists, medication dispensers) in the facility. When HIV testing is done among individuals showing signs or symptoms of HIV/AIDS, it's diagnostic testing and therefore **it's not** considered a form of active testing (or screening) even if it is provider-initiated. Some examples of programmatic strategies which are types of active testing include: 1) asking all patients to bring their sex partner(s) for HIV-testing, 2) "Prevention-with-Positives" program where HIV-positive patients encourage individuals of unknown HIV-status to get tested, 3) Provider Initiated Testing and Counseling (PITC) where providers in health facilities periodically initiate HIV testing among all asymptomatic individuals of unknown HIV status independent of the reason they are seeking health care. Which of the following describes this facility most accurately at this moment?	Active testing has never been practiced at this facility as defined on the left. Choose this option if, **for example**, active testing has never been part of the protocol or implemented at this facility.	1→	B12
		Active testing has been practiced at this facility, as defined on the left, but the coverage has been limited. Choose this option if, **for example**, as part of the facility's standard protocol, active testing strategies have been implemented in an attempt to test asymptomatic, undiagnosed relatives, sex partner(s), or other household members of enrolled patients. However, historically few providers (e.g. less than half) have followed this protocol and/or the protocol has been implemented for less than half the time this facility has been operating.	2	
		Active testing has been practiced at this facility, as defined on the left, and coverage has been high. Choose this option if, **for example**, as part of the facility's standard protocol, active testing strategies have been implemented in an attempt to test asymptomatic, undiagnosed relatives, sex partner(s), or other household members of enrolled patients. Moreover, historically the majority of providers (e.g. 50% or more) have followed this protocol **and** the protocol has been implemented for more than half the time this facility has been operating.	3	
		Other (describe here) _____ _____ _____ _____ _____ _____	4	

No.	Questions and Instructions	Responses	Skips
B02	If active testing for HIV has ever been practiced at this facility, in which populations has active testing been conducted or targeted? (Please check all that apply)	Yes / No / Don't Know a. *Relatives of enrolled patients* ☐ ☐ ☐ b. *Sex partner(s) of enrolled patients* ☐ ☐ ☐ c. *Other household adults of enrolled patients* ☐ ☐ ☐ d. *Children (16 yrs old and under) of enrolled patients* ☐ ☐ ☐ e. *Other (describe)*_____ ☐ ☐ ☐	
B03	Please list all of the active testing strategies which have been formally implemented at this facility, and the time during care (E=at enrollment, F=during follow-up visits, B=both at enrollment and during follow-up visits) where the facility's standard protocol calls for their application	*Active testing method(s)* / Time (E, F, B) 1 _____ _____ 2 _____ _____ 3 _____ _____ 4 _____ _____	
B04	When did implementation of active testing begin in earnest at this facility (i.e. not simply when it became part of the facility's protocol but rather when implementation of the strategy(ies) began?	*Please use the date format MM/YYYY. If multiple active testing strategies have been used at this facility please list the date for when the first method was initiated in earnest.* ☐☐/☐☐☐☐ **If the month is unknown please enter "99" for the month.**	
B05	Since implementation began in earnest, has active testing been completely stopped and not re-initiated?	Yes 1 No 2→ Don't Know 3→	B07 B07
B06	When was it stopped at this facility without subsequent re-initiation?	*Please use the date format MM/YYYY* ☐☐/☐☐☐☐ **If the month is unknown please enter "99" for the month.**	
B07	Are providers supplied with any tools (e.g. family testing form) to facilitate the active testing method(s) employed at this facility?	Yes 1 No 2 Don't Know 3	

No.	Questions and Instructions	Responses		Skips
B08	The level of HIV/AIDS-related stigma in a community can hinder the willingness of patients to bring in or refer others for testing (since patients may fear that it may lead to disclosure or suspicion of HIV/AIDS) and/or asymptomatic individuals to learn their status. Based on your observations, do you believe stigma has substantially limited the uptake of active testing in this facility and its catchment area?	Yes No Don't Know	1 2→ 3→	 B11 B11
B09	If you answered "Yes" to question B08, have you noticed a change in the uptake of active testing over the years?	Yes No Don't Know	1 2→ 3→	 B11 B11
B10	If you answered "Yes" to question B09, when did a change (increase or decrease) in the uptake occur?	*Please use the date format **MM/YYYY** or **for this particular question, if the month is unknown please enter the season for the month: SP** for spring; **SM** for Summer; **FA** for Fall; **WI** for winter along with the year.* ☐☐ / ☐☐☐☐		
B11	Using the space on the right, please describe anything you would like to add regarding the facility's experience with active testing since its implementation to the present date (e.g. based on question B10, if a change was observed was there an increase or decrease in uptake; how successful or unsuccessful has active testing been implemented; period(s) during which active testing has been interrupted temporally since implementation began;). You may use qualifiers such as "very", "modest", "poorly" to describe the degree of success, and "first few years", "most of the time" etc to describe time periods active testing has been interrupted if more specific data (e.g. dates) are not available.			

No.	Questions and Instructions	Responses		Skips
B12	Does this facility provide HIV testing onsite?	Yes No Don't Know	1 2 3	
B13	In some areas, HIV/AIDS workers visit households in the community to offer HIV testing (home-based voluntary counseling and testing). Has there ever been such a program in this facility's catchment area?	Yes No Don't Know	1 2→ 3→	 C01 C01
B14	If you answered "Yes" to question B13, when has each round of home-based voluntary counseling and testing taken place in this facility's catchment area?	*Please use the date format MM/YYYY or* ***for this particular question, if the month is unknown please enter the season for the month: SP*** *for spring;* ***SM*** *for Summer;* ***FA*** *for Fall;* ***WI*** *for winter along with the year.* ☐☐/☐☐☐☐ ☐☐/☐☐☐☐ ☐☐/☐☐☐☐ ☐☐/☐☐☐☐ **If the month is unknown please enter "99" for the month.** Don't Know	 3	
B15	If you answered "Yes" to question B13, has this facility ever been linked to a home-based voluntary counseling and testing program?	Yes No Don't Know	1 2→ 3→	 C01 C01
B16	If this facility has ever been linked to a home-based voluntary counseling and testing program, when was it linked? (e.g. 02/2002-Present, 03/2004-07/2005)	*Please use the date format MM/YYYY* ☐☐/☐☐☐☐ *To* ☐☐/☐☐☐☐ **If the month is unknown please enter "99" for the month.**		

Program Characteristics Part 2: The following questions pertain to the approach (family-focused care or other models) used to deliver HIV/AIDS care and treatment at this facility.

No.	Questions and Instructions	Responses		Skips
C01	The **family-focused care model** aims to involve (and when needed, provide health care to) relatives, sex partner(s), and other household members in the care and treatment of their respective enrolled patient(s). Although it shares a similarity with active testing by asking enrolled patients to bring in sex partner(s) and other household members for HIV testing, family-focused care often goes beyond that by, for example, a) involving HIV-negative sex partner(s), relatives and/or household members in the care of enrolled patients (e.g. for emotional support), b) providing HIV/AIDS prevention and care services to enrolled patients and their family, c) encouraging providers to focus on the health needs of the family not just the individual patients. Thus, although it is common for facilities which follow a family-focused care model to also practice active testing, active testing may be practiced in facilities that do not follow a family-focused care model. MTCT-Plus facilities are one example of facilities following the family-focused care model. On the other hand, pMTCT facilities are not unless they also extend HIV/AIDS care to other family members in addition to the HIV-positive mother and her baby Which of the following describes the model of care followed by this facility most accurately at this moment?	This facility has not followed the family-focused care model as defined on the left. Its primary focus has been on the enrolled patients, and although disclosure of HIV status may be encouraged, it is not part of the facility's protocol to involve HIV-negative family members in the care of enrolled patients. Choose this option if, **for example**, although this facility would treat HIV-positive relatives, sex partner(s) and household members of patients when they seek care, it has not been the facility's standard protocol to provide comprehensive care to enrolled patients and their family.	1→	C09
		This facility has adopted a family-focused care model, as defined on the left, but HIV/AIDS services have been highly individually-focused. Choose this option if, **for example**, the facility's standard protocol has been to follow the family-focused care model. However, historically few providers (e.g. less than half) have followed this protocol and/or the protocol has been implemented for less than half the time this facility has been operating.	2	
		This facility has followed a family-focused care model, as defined on the left, and services are truly family focused. Choose this option if, **for example**, the facility's policy a) called for providers to proactively reach out to relatives, sex partner(s) and household members (including those who are HIV-negative) to support their respective patients, b) aimed to schedule together facility visits of enrolled patients, their children, and sex partner; and c) historically most providers (e.g. 50% or more) have followed this policy **and** the protocol has been implemented for more than half the time this facility has been operating. .	3	
		Other (describe here) _____ _____ _____ _____ _____	4	

No.	Questions and Instructions	Responses	Skips
C02	If this facility has ever followed a family-focused care model, to which populations is HIV care and treatment systematically offered? (Please check all that apply)	Yes No Don't Know a. *Relatives of enrolled patients* ☐ ☐ ☐ b. *Sex partner(s) of enrolled patients* ☐ ☐ ☐ c. *Other household adults of enrolled patients* ☐ ☐ ☐ d. *Children (16 yrs old and under) of enrolled patients* ☐ ☐ ☐ e. *Other (describe)*_____ ☐ ☐ ☐	
C03	When did implementation of the family-focused care model begin in earnest at this facility (i.e. when providers began to follow the family-focused care model not simply when the policy went into effect)?	*Please use the date format MM/YYYY* ☐☐/☐☐☐☐ **If the month is unknown please enter "99" for the month.**	
C04	Since implementation of the family-focused care model began in earnest, has it been stopped and not re-initiated?	Yes 1 No 2→ Don't Know 3→	 C06 C06
C05	If you answered "Yes" to question C04, when was the family-focused care model stopped at this facility without subsequent re-initiation?	*Please use the date format MM/YYYY* ☐☐/☐☐☐☐ **If the month is unknown please enter "99" for the month.**	
C06	Social factors such as the level of stigma in the community can deter patients from involving their family in their HIV/AIDS care even when a facility follows a family-focused care model. Based on your observations, do you believe stigma in the community has substantially prevented this facility from focusing on the health of the family not just individual patients?	Yes 1 No 2→ Don't Know 3→	 C09 C09
C07	If you answered "Yes" to question C06, have you noticed a change in the proportion of patients willing to involve their family in their care?	Yes 1 No 2→ Don't Know 3→	 C09 C09
C08	If you answered "Yes" to question C07, when did a change (increase or decrease) occur?	*Please use the date format MM/YYYY or for this particular question, if the month is unknown please enter the season for the month: SP for spring; SM for Summer; FA for Fall; WI for winter along with the year.* ☐☐/☐☐☐☐	

No.	Questions and Instructions	Responses		Skips
C09	Is it part of this facility's practice to document the family ties (i.e. relationship between patients and their respective sex partner(s), relatives and other household members receiving care in the same facility) among enrolled patients and their relatives, children, sex partner(s), and other household members?	Yes No Don't know	1 2→ 3→	 C11 C11
C10	When did the practice of documenting family ties begin in earnest at this facility?	*Please use the date format MM/YYYY* ☐☐/☐☐☐☐ **If the month is unknown please enter "99" for the month.**		
C11	Has this facility ever been part of the MTCT-Plus Initiative?	Yes No Don't Know	1 2→ 3→	 C13 C13
C12	If you answered "Yes" to question C11, when was it part of the MTCT-Plus initiative? (e.g. 02/2002-Present, 03/2004-07/2005)	*Please use the date format MM/YYYY* ☐☐/☐☐☐☐ *To* ☐☐/☐☐☐☐ **If the month is unknown please enter "99" for the month.**		
C13	Is it part of this facility's protocol to encourage its HIV-positive patients to disclose their HIV-status to relatives, sex partner(s) and/or other household members?	Yes No Don't Know	1 2→ 3→	 C16 C16
C14	If you answered "Yes" to Question C13, does this facility provide supportive services to encourage disclosure of HIV status (e.g., patient counseling, couple counseling around disclosure)?	Yes No Don't Know	1 2 3	
C15	When did providers at this facility begin in earnest to encourage its HIV-positive patients to disclose their HIV-status to relatives, sex partner(s) and/or household members (i.e. not simply when disclosure became part of the facility's protocol but when providers began encouraging enrolled patients to disclose their HIV-status)?	*Please use the date format MM/YYYY* ☐☐/☐☐☐☐ **If the month is unknown please enter "99" for the month.**		

No.	Questions and Instructions	Responses	Skips
C16	Please add any other relevant information about the family-focused care program followed at this facility (this could include your assessment of its effectiveness; whether it has been implemented sporadically; changes over the years in the proportion of patients disclosing their HIV-status to household members and willingness to involve their relatives in the family-focused approach; do enrolled patients support family-focused care etc).		